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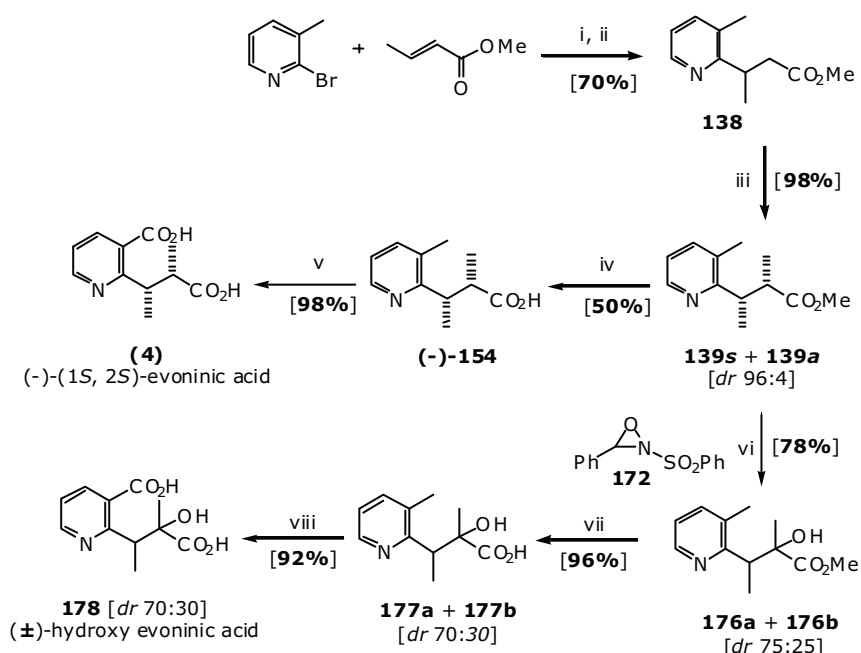
The Synthesis of Evoninic Acids

**A Thesis Submitted in Partial Fulfilment for the
Degree of Ph.D.**

Lena Shukla

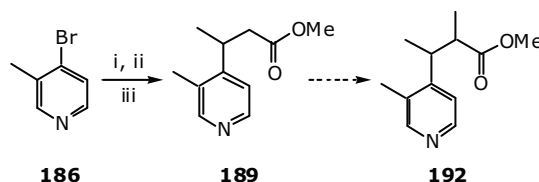
Abstract

The 1,4-addition of 2-, and 4-pyridyl cuprates to enones, enoates and unsaturated nitriles have been shown for the first time to be synthetically useful, obtaining the 1,4-addition products in high yields. This methodology has enabled an expedient, highly diastereo- and enantioselective synthesis of (-)-evoninic acid (**4**), using a lipase mediated hydrolytic kinetic resolution step to control the absolute stereochemistry. Model studies made towards the synthesis of hydroxy-*iso*-evoninic acid have established the synthesis of the un-natural product hydroxy evoninic acid **178**.



Reagents and conditions: (i) *n*-BuLi, Et₂O, -78 °C; (ii) CuI, SBU₂, 0 °C; (iii) KHMDS, MeI, Tol, -78 °C; (iv) Lipase P. Fluorecens, potassium phosphate pH 7.0 buffer, 37 °C; (v) KMnO₄, H₂O, 100 °C; (vi) KHMDS, Oxaziridine **172**, 25 °C; (vii) NaOH, MeOH, 60 °C; (viii) KMnO₄, H₂O, 100 °C

The synthesis of hydroxy *iso*-evoninic acid using a strategy analogous to that used for the synthesis of hydroxy evoninic acid was also investigated. Unfortunately, installation of the methyl group α to the ester in substrate **189** through a variety of methods proved to be impossible.



Reagents and conditions: (i) *n*-BuLi, Et₂O, -78 °C; (ii) CuI, SBU₂, Et₂O, 0 °C; (iii) Methyl crotonate

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1 Abbreviations

Ac	acetyl
acac	acetylacetonate
Anal.	analysis
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
b.p.	boiling point
br	broad
Bu	butyl
°C	degrees Celsius
c.	concentrated
calcd	calculated
CAN	ceric ammonium nitrate
cat.	catalytic
CD	circular dichroism
CI	chemical ionisation
Cod	cyclooctadiene
Conc.	concentrated
d	doublet
DMF	<i>N,N</i> -dimethylformamide
DMG	directed metalation group
DMSO	dimethylsulfoxide
DoM	directed <i>ortho</i> -metalation
dppb	1,4-bis(diphenylphosphino)butane
<i>dr</i>	diastereoisometric ratio
e.e.	enantiomeric excess
e.g.	<i>exempli gratia</i> (Latin: 'for example')
EI	electron impact
eq.	equivalent(s)
ES	electrospray
Et	ethyl
g	gram(s)
GS-MS	gas chromatography – mass spectrometry
hr	hours
IC ₅₀	inhibitory concentration (that is needed to kill 50% of cells <i>in-vitro</i>)

<i>I</i>	<i>iso</i>
<i>i.e.</i>	<i>id est</i> (Latin: 'that is')
IR	infra-red spectroscopy
<i>J</i>	coupling constant
K	Potassium
KHMDS	Potassium hexamethyldisilamide
L	litre
LDA	lithium diisopropylamide
Li	Lithium
m	multiplet
M	molar (concentration: 1 mol/L)
<i>m</i>	<i>meta</i>
Me	methyl
mL	millilitre(s)
mmol	millimole(s)
mg	milligram(s)
m.p.	melting point
MS	mass spectrometry
Mol. sieves	molecular sieves
MVK	methyl vinyl ketone
<i>n</i>	<i>normal</i>
Na	Sodium
NBS	<i>N</i> -bromosuccinamide
NMR	nuclear magnetic resonance
<i>o</i>	<i>ortho</i>
p	para
Ph	phenyl
ppm	parts per million
Pr	propyl
Pyr	pyridine
q	quartet
quin	quintet
R	general substituent
Rh	rhodium
rt	room temperature
s	singlet
sat.	saturated
sec	secondary

SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
<i>t</i>	<i>tertiary</i>
TBS	<i>tert</i> -butyldimethyl silyl
Temp.	temperature
Tf	trifluoromethanesulfonyl (triflic)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
UV	ultraviolet

2 Introduction

2.1 Evoninic Acids

2.1.1 Brief History

Crude extracts of *Tripterygium* Celastraceae have been used in traditional Chinese remedies for many hundreds of years, notably for the treatment of cancers. They have also been used extensively as insecticides.^{1,2} Celastraceae plants are indigenous to many northern provinces of Africa, parts of eastern Asia and South America.² The most pervasive bio-active secondary metabolites found in these plants are a large family of sesquiterpene alkaloids. This class of alkaloids has generated a substantial amount of interest to academic and medicinal chemists alike, largely because of their diverse and potent biological activity against a wide range of therapeutic targets.²

In 1998, Takaishi described the isolation of hypoglaunine B (**1**) (**Fig 2.1.1.1**), along with several other related sesquiterpenes, including hypoglaunines A, C and D.¹

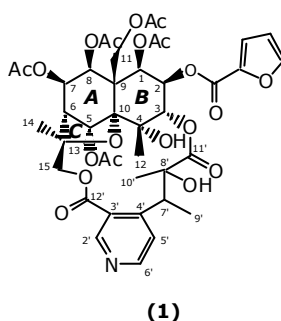


Figure 2.1.1.1– Structure of hypoglaunine B (**1**) with ring labelling and numbering.

The product was isolated from the ethyl acetate soluble fractions of methanolic extracts from the root bark of *Tripterygium hypoglaucum*. The structure was found to contain a euonyminol sesquiterpene core comprising of an A- and B-ring system, in the form of an axially dimethylated *trans*-decalin bicycle, with a 1,3-diaxially fused, Me₂C-O bridge, constituting the tetrahydrofuran C-ring.² Additionally, it was found to contain a macrodilactone that bridged between C3 and C15. The ¹H NMR (**Table 2.1.1.1**) identified the structure of hypoglaunine B as also containing five acetyl esters, a 2-furanoyl ester and the aforementioned lactone bridge containing a pyridyl fragment. The ¹³C NMR (**Table 2.1.1.2**) provided the most vital data, allowing for the structural assignments of the macrocycle with respect to the other peripheral groups. Takaishi later

demonstrated that hypoglaunine B exhibited significant anti-HIV activity.³ It is thought to act by inhibiting HIV virus replication in H9 lymphocytes, and displays an EC₅₀ of 0.10 µg/mL and a therapeutic index of >1000^{3,4} - this level of activity is uncommon in a bioactive compound from a natural source.

Proton	¹ H NMR δ
1-H	5.68 (d, 3.9)
2-H	5.54 (dd, 2.4, 3.9)
3-H	4.79 (d, 2.4)
5-H	7.05 (s)
6-H	2.42 (d, 3.9)
7-H	5.53 (dd, 3.9, 6.3)
8-H	5.39 (d, 6.3)
11-H'	4.29 (d, 13.6)
11-H''	5.48 (d, 13.6)
12-H3	1.56 (s)
14-H3	1.63 (s)
15-H'	4.29 (d, 11.7)
15-H''	5.14 (d, 11.7)
2'-H	9.00 (s)
5'-H	7.83 (d, 4.9)
6'-H	8.69 (d, 4.9)
7'-H	4.24 (q, 6.8)
9'-H3	1.19 (d, 6.8)
10'-H3	1.38 (s)
1-Ac	2.20 (s)
5-Ac	2.18 (s)
7-Ac	1.98 (s)
8-Ac	1.85 (s)
11-Ac	2.33 (s)

Table 2.1.1.1 - ¹H NMR of
Hypoglaunine B

Carbon	¹³ C NMR δ
1	73.0
2	68.3
3	77.9
4	71.7
5	74.7
6	51.1
7	69.3
8	71.2
9	52.8
10	93.6
11	60.6
12	22.8
13	83.6
14	18.7
15	69.9
2'	151.7
3'	127.7
4'	152.0
5'	123.6
6'	152.7
7'	42.3
8'	77.1
9'	17.4
10'	24.2
11'	175.2
12'	167.7
1-Ac	21.5, 169.5
5-Ac	20.9, 169.8
7-Ac	20.4, 168.8
8-Ac	20.3, 169.0
11-Ac	21.2, 170.6

Table 2.1.1.2 - ¹³C NMR of hypoglaunine B

Hypoglaunine B can be considered to be comprised of two major components: a euonyminol derivative **2**⁵⁻⁹ and hydroxy *iso*-evoninic acid (**3**) (**Fig 2.1.1.2**).^{2,10}

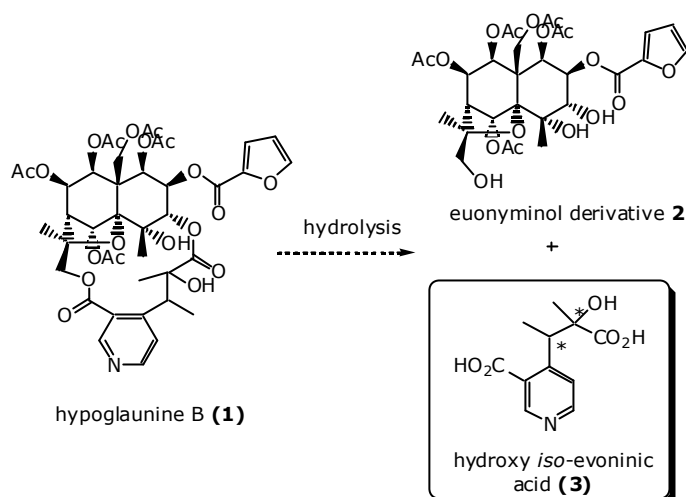


Figure 2.1.1.2 – Hypothetical degradation of hypoglaunine B (**1**).

The first and only total synthesis of (±)-euonyminol was described by White in 1997.⁹ More recently, Spivey has described the enantioselective desymmetrisation of *meso*-decalin diallylic alcohols,¹¹ with the intention of applying this methodology to the first asymmetric synthesis of (-)-euonyminol. (±)-Hydroxy *iso*-evoninic acid (**3**) on the other hand, has not been isolated and thus no analytical data has been directly reported on this compound. However, it is one in a series of related esterifying residues that are found on the periphery of the polyhydroxy dihydroargofuran cores of Celastraceae sesquiterpenoids (**Fig 2.1.1.3**).

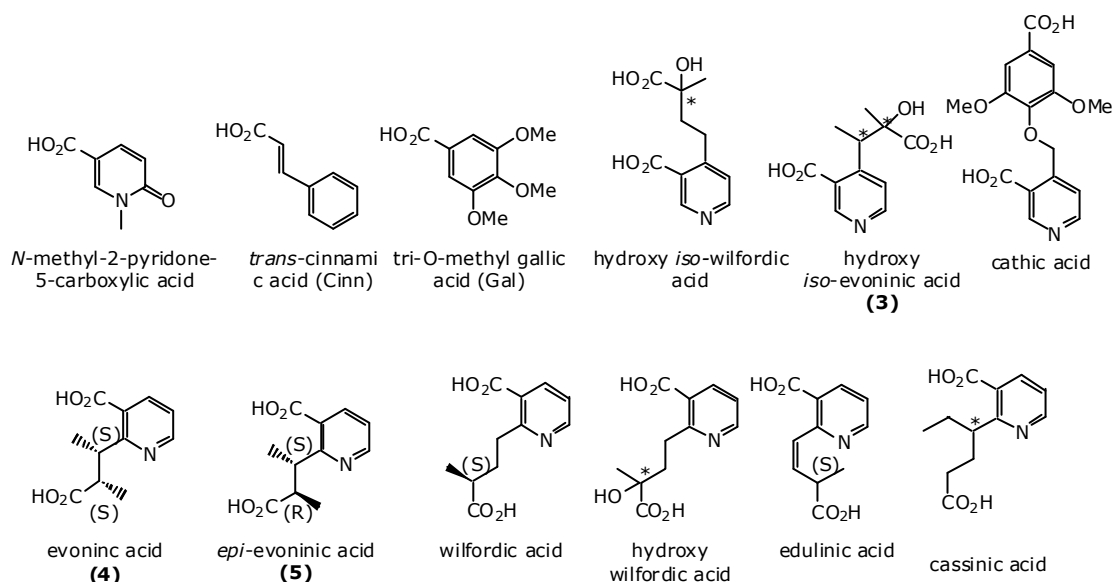


Figure 2.1.1.3 – Some examples of esterifying residues found in Celastraceae natural products.

The most widely documented residue from this family of diacids is (-)-evoninic acid (**4**). (-)-Evoninic acid was first isolated by Pailer and Libeseller in 1962,^{12,13}

as a degradation product of evonine (**6**). The hydrolysis of Evonine (**Fig 2.1.1.4**) followed by a transesterification of the pyridyl fragment with MeOH yielded (-)-evoninic acid as its dimethyl ester. UV spectroscopy of this residue suggested that it was a pyridine derivative. ^1H and ^{13}C NMR data defined the structure as drawn above and the relative stereochemistry as being *syn* with respect to the methyl groups. The absolute stereochemistry was confirmed as 1*S*, 2*S* by correlation of the sign of optical rotation of the dimethyl ester following degradation, with that of glyceraldehydes, $[\alpha]_{\text{D}}^{20} -42$ (CHCl_3).¹⁴ An X-ray analysis of bromoacetylneovonine (**7**) (**Fig 2.1.1.5**) also supported the proposed structure.¹⁵ Others, subsequently reported more detailed NMR and mass spectra data for (-)-evoninic acid, which irrefutably supported the original findings.^{16,17}

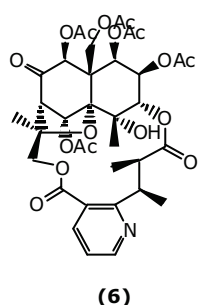


Figure 2.1.1.4 – Evonine (6)

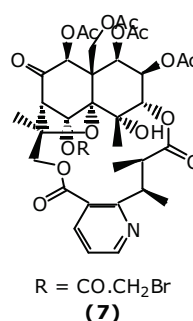


Figure 2.1.1.5–Bromoacetylneovonine (7)

(-)-Evoninic acid is prevalent in a number of biologically active *Celastraceae* alkaloids. Of particular interest is Emarginatine F (**8**) isolated by Kuo from the crude extracts of *M. emarginata* in 1994. It displays significant cytotoxicity against human KB cells (*anti* tumor) having an ED₅₀ of 1.29 $\mu\text{g/mL}$ (**Figure 2.1.1.6**).¹⁸

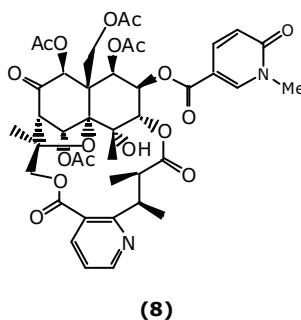


Figure 2.1.1.6 – Emarginatine F (8)

2.1.2 Biosynthesis

The proposed biosynthesis for the family of pyridine diacids, is generally thought to be from nicotinic acid (**9**) or nicotinamide adenine dinucleotide, NAD.¹⁹ The *in vivo* mechanism has been suggested to involve a radical coupling process between a nicotinate derivative and a C₅ *iso*-leucine derivative **10** (Fig 2.1.2.1). It is thought that the radical centre is generated on the *iso*-leucine derivative **10** and attacks at either the C2- or C4-position of the nicotinate species to yield the diacids. Evoninic acid (**4**) is substituted at the C2-position of the pyridine ring, having a 1*S*, 2*S* configuration at the chiral centres. Similarly, *epi*-evoninic acid (**5**) is substituted at the C2-position of the pyridine ring and has a 1*S*, 2*R* configuration at the chiral centres. Hydroxy *iso*-evoninic acid (**3**), on the other hand, is substituted at the C4-position of the pyridine ring, with the absolute and relative stereochemistry yet to be determined for the natural product, hypoglaunine B (**1**).² This diacid also varies from the others, as it contains a hydroxyl group α to the non-benzylic acid. The presence of a hydroxy group is more commonly seen in the esterifying residues of the wilfordic family of acids.^{2,20,21}

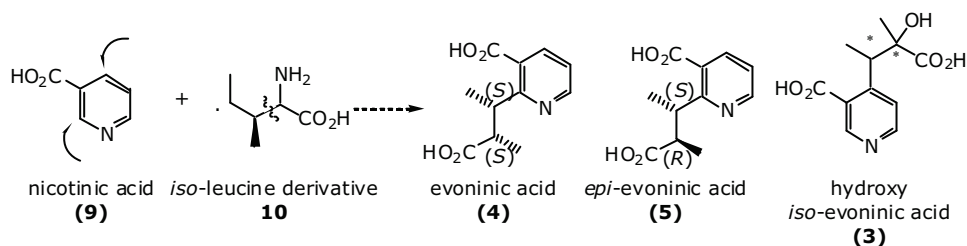
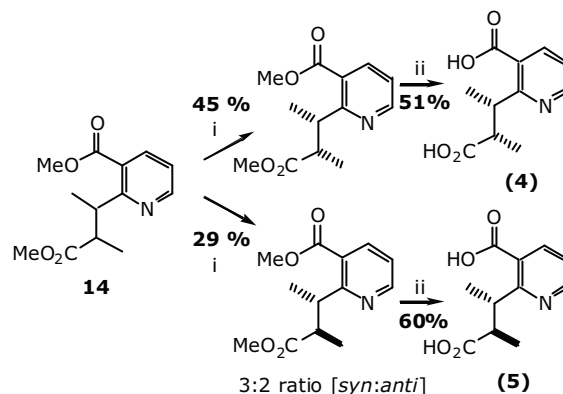
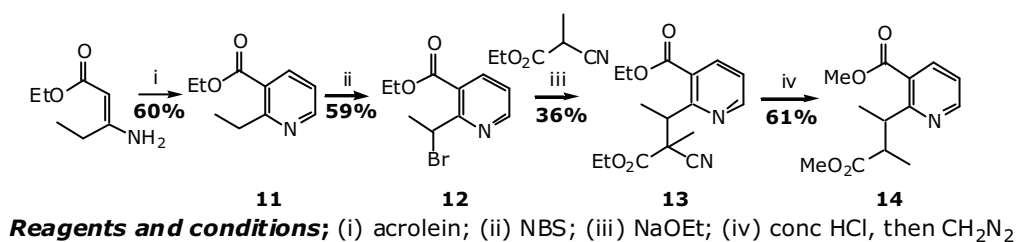


Figure 2.1.2.1 – Proposed biosynthesis of the evoninic family of diacids.

2.1.3 Synthetic Precedent

Prior synthetic work in this area is limited to just one report. In 1976, Pailer and Pfleger described the synthesis of ($\pm$)-evoninic acid (**4**).²² The synthesis involved taking an β -amino substituted α,β -unsaturated ester, and conducting a condensation-cyclisation reaction with acrolein to afford the 2-ethyl nicotinate product **11**. The nicotinate derivative was then brominated with NBS to form the bromide **12**, which was treated with methyl cyanoacetate to give the alkylated product **13**. The ester was then subjected to hydrolysis and decarboxylation to give the corresponding diacids, which immediately treated with diazomethane to the dimethyl esters **14**. After the diastereoisomers were separated by gas chromatography, the products were hydrolysed to give ($\pm$)-evoninic acid (**4**) and ($\pm$)-*epi*-evoninic acid (**5**) in a 3:2 ratio (*syn:anti*) (Scheme 2.1.3.1).¹⁰



Scheme 2.1.3.1 - Pailer and Pleger's synthesis of evoninic acid and *epi*-evoninic acids.

The major limitation of this approach is that the synthesis is low yielding, displays poor diastereoselectivity and is racemic.

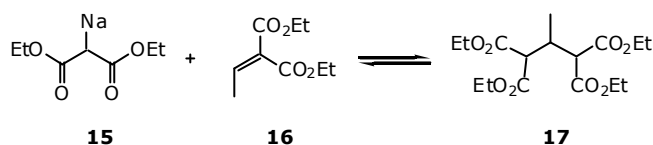
The key step in our synthetic strategy (see '**Aims and Objectives of the Project**') involves the enantioselective 1,4-addition of a pyridyl metal derivative to an α,β -unsaturated ester. It is well documented that the most efficient methods for the addition of aryl substrates to unsaturated compounds are either by chiral auxiliary-controlled organocopper addition chemistry or by the employment of rhodium catalysed asymmetric 1,4-addition. The following sections overview these areas.

2.2 1,4-Addition

A 1,4-addition reaction can be defined as the addition of a nucleophile to an unsaturated system in conjugation with an activating group, usually an electron-withdrawing group. In general, the electron-withdrawing group serves to activate the double bond towards nucleophilic attack. The nucleophile approaches the double bond so as to interact with the $\pi^*_{C=C}$ orbital and the resulting carbanion is stabilised by the electron-withdrawing group.²³

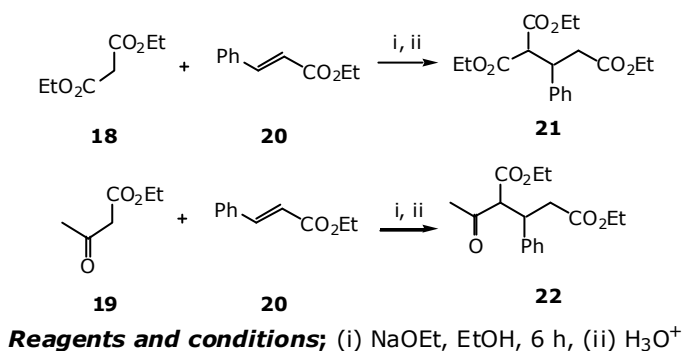
2.2.1 A Brief History

In 1883, Komnenos reported the first example of a 1,4-addition reaction.²⁴ He described the addition of diethyl sodiomalonate **15** to diethyl ethylidene malonate **16** (Scheme 2.2.1.1).



Scheme 2.2.1.1 – Komnenos' reaction between diethyl sodiomalonate and diethylidene malonate, 1883.

The reaction proceeded in one-pot to exclusively yield the 1,4-addition product **17**. However, it was Michael in 1887 who refined this chemistry,²⁵ when he described the base promoted addition of sodium salts of diethyl malonate **18** and ethyl acetoacetate **19** salts to ethyl cinnamate **20** to yield the 1,4-adducts **21** and **22**, respectively (Scheme 2.2.1.2).



Scheme 2.2.1.2 – Michael's reactions of sodium malonate and ethyl acetoacetate with ethyl cinnamate, 1887.

As a result of this early work, there has been a substantial amount of research done in this area;²⁶ which has developed and extended the protocol to accomplish more elaborate and advanced syntheses, to include the total synthesis of important natural products, such as antibiotics²⁷ and steroids.²⁸ The 1,4-addition of organometallic reagents to enones is now one of the most powerful tools for appending organic residues to cyclic and acyclic substrates by the formation of a new C-C sigma bond.²⁹ The most widely documented are the use of organocopper²⁹⁻³¹ or organozinc^{29,31} complexes, which have dominated the field for many years.

2.2.2 Regiochemistry – 1,2- vs 1,4-Addition

The regiochemistry of a 1,4-addition reaction (i.e. 1,2 vs. 1,4) can be dependent upon a range of factors, but under thermodynamic conditions the 1,4-addition product is favoured (*cf.* strengths of the C=O vs. C=C bonds). One of the

governing factors is the type of nucleophile participating in the reaction; which are normally classified as “hard” or “soft”.²³ Soft nucleophiles will usually undergo 1,4-addition transformations. Soft nucleophiles are neutral species or ones in which the charge is delocalised or diffuse. Examples include radical anions, sulfur-, selenide-, or tin enolates, doubly activated enolate anions (e.g. malonates), bis nitriles and bis sulfones. Soft nucleophiles have high energy HOMO's, whereas hard nucleophiles have low energy HOMO's.²³

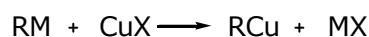
2.3 Copper Based 1,4-Addition Reactions

Most organometallic reagents are hard nucleophiles and participate in 1,2-addition reactions. However, an important class of compounds has been developed which exhibit *soft* behaviour; these are copper based reagents. Copper based organometallic reagents are invariably soft and undergo 1,4-addition reactions.

2.3.1 Organocopper Reagents

There are several different types of organocopper reagents, which are used in synthesis for 1,4-addition reactions.²³

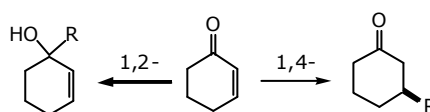
- (1) *Mono-organocopper reagents (RCu)* – these are prepared by treatment of a Grignard or organolithium reagent with a copper salt (**Scheme 2.3.1.1**).



Scheme 2.3.1.1 – General scheme for the synthesis of mono-organocopper reagents.

Additionally, they can be prepared and reacted *in-situ*. The wider use of organocopper chemistry was retarded due to the lack of reproducibility of results.

- (2) *Catalytic cuprate (RM + <25 mol % CuI)* – treatment of Grignard reagents with a catalytic amount of a copper salt (RMgX, 0.2 mol % CuI) can lead to a profound change in reactivity, resulting in a 1,4-addition transformation in place of the expected 1,2-addition (**Scheme 2.3.1.2**).



Reagents and conditions; (i) MeMgBr (ii) MeMgBr, CuI

Scheme 2.3.1.2 – Effect of adding a copper salt to a Grignard reaction.

- (3) *Lower-order organocuprates* ($R'RCu^+M^+$) – there are several categories of lower-order cuprates. (i) homocuprates R_2CuLi (ii) mixed homocuprates $RR'CuLi$ where $R \neq R'$ and (iii) heterocuprates $RR'CuLi$ where $R' = CN$ or inorganic (**Scheme 2.3.1.3**).



Scheme 2.3.1.3 – General Scheme for the synthesis of lower-order cuprates.

Only one of the R groups is transferred, thus the cuprate reagent is wasteful and may not transfer the required group. Reagents have been designed such that one of the ligands does not transfer and are so called the *dummy* ligands (e.g. alkynes, alkyl thiophenyl).

- (4) *Higher-order organocuprates* [$RR'Cu(CN)Li_2$, R_3Cu_2Li , $R_5Cu_3Li_2$ and R_3CuLi_2] – prepared by the addition of two or more equivalents of an organolithium reagent to copper cyanide. Often contain a *dummy* ligand that is non-transferable. (**Scheme 2.3.1.4**).



Scheme 2.3.1.4 – General scheme for the synthesis of higher-order cuprates.

- (5) *Yamamoto Reagents* ($RCu.BF_3.OEt_2$) – The addition of $BF_3.OEt_2$ is thought to drastically increase the reactivity of organo copper reagents, resulting in an organocuprate with unique properties.

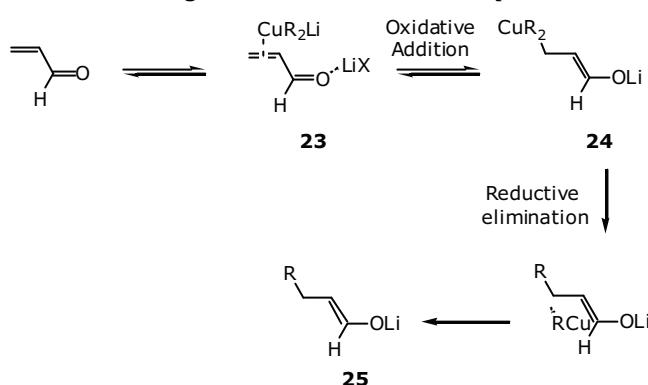
Organocopper complexes are more widely associated with the addition of simple straight chain alkyl motifs, to a wide range of α,β -unsaturated substrates including ketones, aldehydes, amides, esters, nitriles and phosphonates.²³ Not only has this methodology proven to be highly versatile with regards to substrate and reagent, over the last 20 years it has developed into a robust enantioselective strategy where many nucleophiles can now be added with good stereochemical control when used in combination with an appropriate acyl chiral auxiliary.²⁹

In order to utilise this methodology to its full potential, it is important to gain a better understanding of the reaction mechanism. The following section discusses the proposed catalytic cycle and the associated supporting evidence.

2.3.2 Reaction Mechanism

The organocopper 1,4-addition reaction mechanism has been widely debated in the literature.³²⁻³⁵ A considerable amount of experimental and theoretical evidence has been collected to determine the exact reaction coordinate. There have been a number of comprehensive reviews published in this area; which details much of the work done so far. In view of this, the following section intends only to give a brief overview of the key features of the reaction pathway and the supporting evidence.³²⁻³⁴

A combination of kinetic studies, in particular $^{12}\text{C}/^{13}\text{C}$ kinetic isotope effect measurements, and NMR spectroscopy of the intermediates observed during the reaction, suggests the following reaction mechanism (**Scheme 2.3.2.1**).³⁶⁻³⁸



Scheme 2.3.2.1 – Proposed copper catalysed 1,4-addition reaction mechanism.

Evidence supports the formation of a reversible π -complex between the cuprate and the activated olefin (involving $d \rightarrow \pi^*$ back bonding), complex **23**. This complex then undergoes a formal oxidative addition to the β -carbon resulting in the formation of a d^8 Cu(III) intermediate, cuprate **24**. Then by reductive elimination of the cuprate by transferring the R group in the key C-C bond-forming step, the enolate product, complex **25** is formed. Experimental and theoretical studies made by Krause indicate that the rate determining step is the C-C bond formation *via* reductive elimination of the Cu(III) intermediate.³⁸

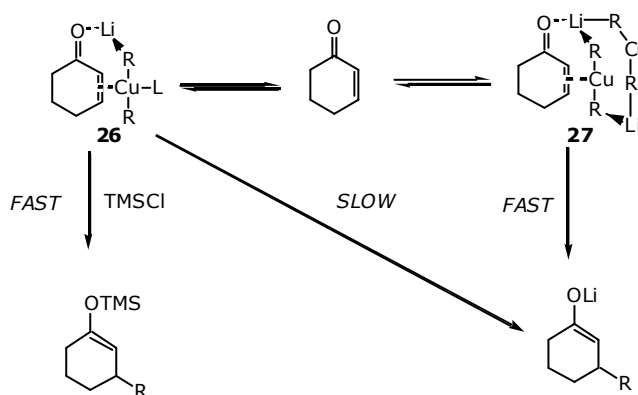
Low temperature studies have proven the existence of π -complexes for α,β -unsaturated ketones, esters and nitriles.³⁹ Controversially the Cu(III) intermediates (recognised as a high energy species); which have been speculated as being transient intermediates along the reaction coordinate, have not yet been directly observed. As a result, the involvement of these species is supported primarily through quantum-chemical calculations.⁴⁰

The addition of additives in the reaction has led to many researchers to postulate variations of the mechanism to account for their role in the reaction, however essentially the same mechanism has been described. Yamamoto described the addition of a mono-organocopper reagent to $\text{BF}_3 \cdot \text{OEt}_2$ to form a new organocopper species with unique properties as previously described. The BF_3 acts a Lewis acid stabilising the Cu(III) intermediate, whilst kinetically labilising the R groups to subsequent reductive elimination. However, other Lewis acids (for example ZnCl_2 , TiCl_4 , SnCl_4 etc.) have been less successful in the reaction due to the formation of an intractable gum with cuprates at low temperature (-78°C).²³

Corey reported that TMSCl accelerated the rate of the 1,4-addition in THF solvent systems. He argued that TMSCl enhanced the rate of the 1,4-addition reaction, by increasing the selectivity of the organocuprate for the conjugated carbonyl compound. TMSCl "spiked" 1,4-addition reactions were also found to be more stereoselective. Of note is that the selectivity has at times been completely reversed using this additive.⁴¹

Further studies into the mechanism suggested two parallel mechanisms were operative, differing only in the nature of the organocuprate present. Bertz argued that the copper species was present in two major conformers: a monomeric **26** and a dimeric **27** species; which differ in reactivity depending on the reaction conditions. Several observations from this study were made (**Scheme 2.3.2.2**):⁴²

- (1) the dimeric species reacted faster than the monomeric one
- (2) the lithium species was more reactive in Et_2O solvent systems
- (3) the reaction in THF was accelerated with the addition of TMSCl
- (4) both the monomeric and dimeric reaction pathways were operative



Scheme 2.3.2.2 – Bertz's postulated copper catalyzed 1,4-addition reaction mechanism.

Conversely, Snyder argued that Cu(III) intermediates were in fact Cu(I) species by natural population analysis.³⁷ He described a neutral tetracoordinate Cu(I) structure as an alternative intermediate in the 1,4-addition reaction process; which excludes the need to consider Cu(III) intermediates. He suggested that this would also provide a more tangible explanation for the acceleratory behaviour of additives in the reaction.⁴³ Supporting his argument is the existence of stable tetracoordinate Cu(I) complexes, for example, CuSC(S)NEt_2 and $[\text{Cu}(\text{CF}_3)_4]^-$, which have been isolated and fully characterised. Additionally, electron count show a d^9 and d^{10} [Cu(II) to Cu(I)] electronic configuration, suggesting perhaps that the species described as a Cu(III) intermediate is in fact a Cu(I)/Cu(II) couple.

The significance of solvent in the 1,4-addition reaction has also undergone considerable evaluation. Nakamura claimed that the solvent has no effect on the reaction coordinate but postulated that the solvent is involved in increasing the activation energy of the key C-C bond-forming step, by reducing the Lewis acidity of the lithium atoms. Additionally, they describe how substituents on the α,β -unsaturated substrate have a marked effect on the activation energy of this key step.⁴⁴

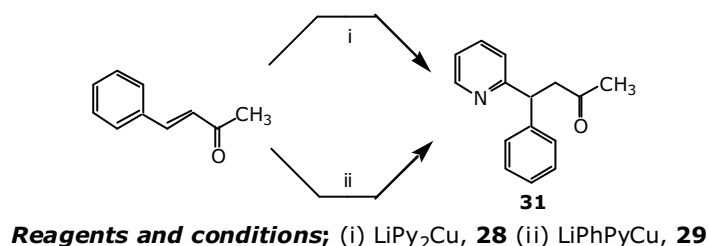
Selective ligand transfer in the 1,4-addition of mixed organocuprates has also been extensively studied. It is thought that the transfer of ligands is primarily dependant on two factors; first the thermodynamic stability of the Cu(III) intermediate formed by π -complexation between the cuprate and the activated olefin, and secondly the kinetic reactivity of this complex. It was found through density functional studies, that for typical 'dummy' ligand the *trans* effect and the strength of the Li-X bond are paramount. Although for less conventional dummy ligands the kinetics of the reductive elimination step come into play.³⁵

Although the exact reaction coordinate of the organocopper 1,4-addition reaction is not completely understood, largely due to lack of hard evidence that Cu(III) intermediates exist; it is clear that the reaction is highly successful for a wide range of substrates, and moreover has been proven to be versatile with regards to aryl cuprates. The following section overviews this area.

2.3.3 Pyridyl Copper Complexes

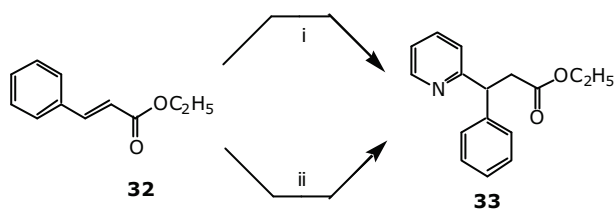
With regards to our synthetic strategy for the synthesis of hydroxy-*iso*-evoninic acid, we are primarily concerned with the 1,4-addition of aryl, heteroaryl and more specifically pyridyl copper complexes. The most common aryl copper reagents to undergo this transformation are unsubstituted phenyl derivatives.⁴⁵ Phenyl groups can be transferred from a range of copper complexes in high yields and with some stereochemical control in the presence of chiral ligands. Conversely, complex aryl and heteroaryl copper complexes are less well described⁴⁵ and therefore have few reports reporting the use of pyridyl copper complexes.

2-Pyridyl copper compounds were first reported as intermediates in an oxidative coupling reaction to give 2,2'-bipyridyl adducts.^{46,47} In 1982 Nilsson examined the utility of these reagents in 1,4-addition reactions. He found that although monopyridyl cuprates (PyCu) were ineffective, homopyridyl cuprate **28** (formed by the addition of two equivalents of pyridyl lithium to a copper salt), and a mixed homocuprate **29** worked well. These pyridyl copper reagents were the first pyridyl cuprates to participate in 1,4-addition to α,β -unsaturated ketones to give ketone **31** in good yield (80-82%) (**Scheme 2.3.3.1**).⁴⁸



Scheme 2.3.3.1 – Nilsson's 1,4-addition of a homo and mixed-homo cuprate to an enone to afford the 1,4-adduct, 1982.

This reaction is significant for our strategy since Nilsson subsequently found that the same homopyridyl cuprate **28** and mixed homopyridyl cuprate **29** could be successfully added to α,β -unsaturated ester **32** to give ester **33** in good yields (74 and 72%, respectively). It is noteworthy that the pyridyl group is preferentially transferred from the mixed homocuprate over the phenyl group (**Scheme 2.3.3.2**).

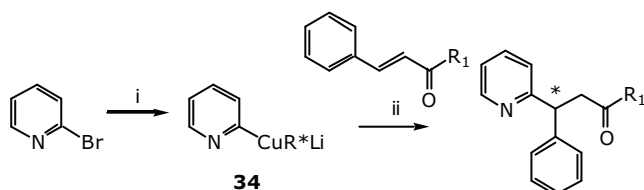


Reagents and conditions; (i) LiPy_2Cu **28**, LiI (ii) LiPhPyCu **29**, LiI

Scheme 2.3.3.2 – Nilsson's 1,4-addition of a homo **28** and mixed-homo **29** cuprate in the presence of a lithium salt to unsaturated ester **32** to afford the 1,4-adduct **33**, 1982.

Additionally, Nilsson noted that the addition of one equivalent of lithium iodide had no effect in the 1,4-addition of these pyridyl cuprates to enones, but was a pre-requisite in the 1,4-addition to α,β -unsaturated esters. It was thought that the lithium iodide closed down the 1,2-addition pathway.

Moreover, Nilsson described the 1,4-addition of lithium chiral mixed homopyridyl cuprates **34** (LiRR^*Cu) to enones in moderate yields. Although optical rotation data were recorded on the products, enantioselectivities were not determined (**Scheme 2.3.3.3**).⁴⁹



$\text{R}^*\text{Li} = (S)\text{-2-(1-dimethylamino)phenyllithium}$

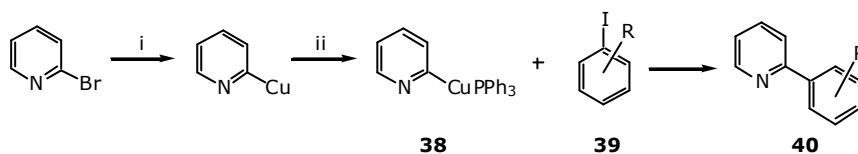
$\text{R}_1 = \text{CH}_3$, 30%, **35**, $t\text{Bu}$, 70%, **36**, OC_2H_5 , 60%, **37**

Reagents and conditions; (i) $n\text{-BuLi}$, CuI , SBu_2 , Et_2O , R^*Li ;
(ii) Et_2O , -45°C

Scheme 2.3.3.3 – Nilsson's synthesis of 2-pyridyl mixed chiral cuprate **34** and subsequent 1,4-addition to α,β -unsaturated compounds, 1983.

These reactions are the first and only asymmetric 1,4-addition reactions of 2-pyridyl cuprates to unsaturated ketones and an ester to give products **35**, **36** and **37** in good yields.

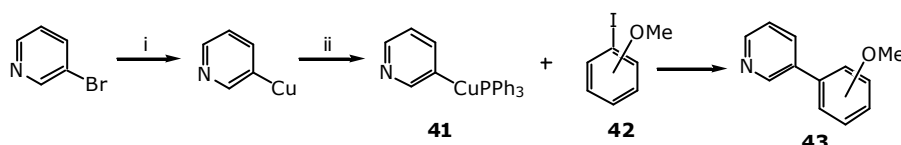
2-Pyridyl copper reagents have also been reported in pyridyl-aryl cross coupling reactions.⁵⁰ Pyridyl copper triphenylphosphine complex **38** was shown to participate in selective heterocoupling with an aryl iodide partner **39** to give the biaryl complex **40** in moderate yields (**Scheme 2.3.3.4**).



Reagents and conditions; (i) $n\text{-BuLi}$, CuI , SMe_2 , Et_2O ; (ii) PPh_3 , Tol

Scheme 2.3.3.4 – Nilsson’s synthesis of a 2-pyridyl copper triphenylphosphine complex **38** and subsequent ary-coupling to iodobenzene **39**, 1986.

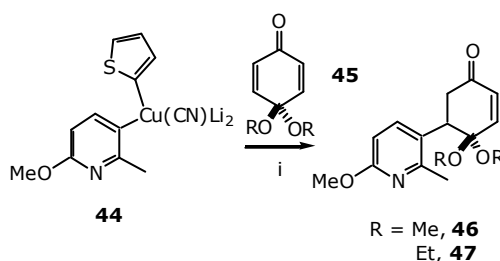
Nilsson also showed that 3-pyridyl copper reagent **41** could be selectively coupled with methoxyiodobenzenes **42** to form biaryls **43** (**Scheme 2.3.3.5**).⁵⁰



Reagents and conditions; (i) $n\text{-BuLi}$, CuI , SMe_2 , Et_2O ; (ii) PPh_3 , Tol

Scheme 2.3.3.5 – Nilsson’s synthesis of a 3-pyridyl copper triphenylphosphine complex and subsequent aryl coupling to methoxyiodobenzene, 1986.

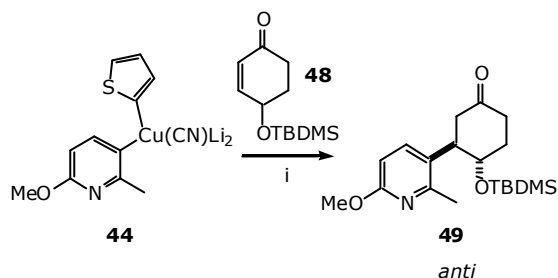
Mann reported the first 1,4-addition reaction of 3-pyridyl higher order cuprate **44** to cyclic enone **45** to afford enones **46** and **47**, albeit in low yields (20 and 10%, respectively) (**Scheme 2.3.3.6**).⁵¹



Reagents and conditions; (i) **45**, Et_2O -THF (1:1), -40°C

Scheme 2.3.3.6 – Mann’s 1,4-addition of a 3-pyridyl higher-order cuprate to enone **45** to give enones **46** and **47**, 1998.

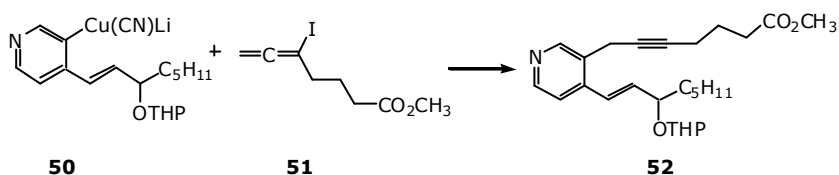
This 3-pyridyl cuprate is *ortho* substituted as required in our synthesis. The low yields were attributed to the low stability of the enone. Addition of the same cuprate **44** to the more stable enone **48** gave the *anti* product **49** in good yield (80%) (**Scheme 2.3.3.7**).



Reagents and conditions; (i) **48**, Et₂O-THF (1:1), -40 °C

Scheme 2.3.3.7 – Mann's 1,4-addition of a 3-pyridyl cyanocuprate **44** to enone **48** to afford the *anti* ketone **49** almost exclusively, 1998.

Corey has also reported the preparation of 3-pyridyl cyanocuprate **50** and its addition to allene **51** in his synthesis of a series of potent inhibitors of thromboxane A₂ biosynthesis.⁵²



Scheme 2.3.3.8 – Corey's addition of 3-pyridyl higher order cuprate **50** to allene **51**, 1983.

Again, this pyridyl cyanocuprate **50** is *ortho* substituted (as required for our synthesis) and gives product **52** in moderate yield (44%).

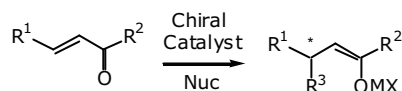
To the best of our knowledge, 4-pyridyl copper complexes are unprecedented in the literature and there are no reports of these reagents undergoing 1,4-addition reactions or any other reactions.

One major limitation with the employment of aryl and alkenylcuprates as reagents in 1,4-addition reactions is that these cuprates are relatively unreactive owing to the strength of the C-Cu bond.^{53,54} This limitation of organocuprate methodology is not shared by transition metal catalysed 1,4-addition reactions. Transition metal catalysts have revolutionised the field, avoiding the use of stoichiometric amounts of copper in these reactions thereby also reducing the environmental impact of the metal.⁵⁵ A chiral ligand on the transition metal can also be used to induce stereoselectivity in these reactions.⁵⁵ For instance, palladium, nickel and copper⁵⁵ complexes partnered with organoaluminium,⁵⁶ organozinc,^{57,58} organozirconium,⁵⁹ organomercury⁶⁰ and organomagnesium (Grignard) reagents, have all shown very promising results.²³

A brief overview of these methods follows:

2.3.4 Catalytic Asymmetric 1,4-Addition

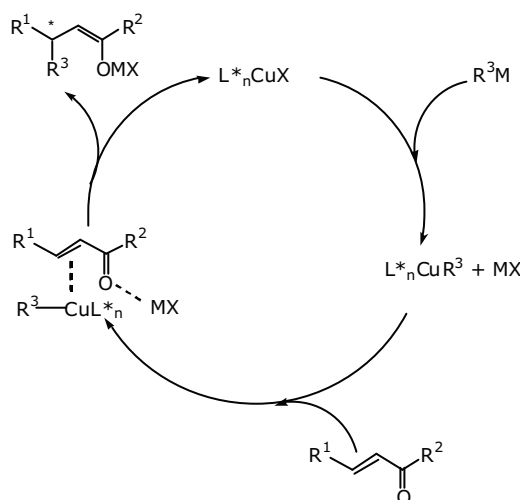
The last decade or so has seen spectacular advances in the transition metal catalysed asymmetric 1,4-addition of various organometallics to α,β -unsaturated substrates (**Scheme 2.3.4.1**).



Typical Nucleophiles - R^3MgX , $(R^3)_2CuLi$, $(R^3)_2Zn$, $(R^3)_3Al$

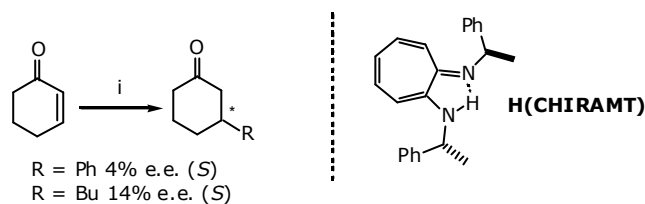
Scheme 2.3.4.1 – General reaction scheme for transition metal catalysed asymmetric 1,4-addition reactions.

The catalytic cycle is thought to proceed *via* a similar mechanism to that postulated for the organocopper 1,4-addition reaction (see **2.3.2 Reaction Mechanism**) except for the fact that the catalyst is now coordinated to a chiral ligand and the copper catalyst is regenerated (**Scheme 2.3.4.2**).



Scheme 2.3.4.2 – General catalytic cycle for transition metal catalysed asymmetric 1,4-addition reactions.

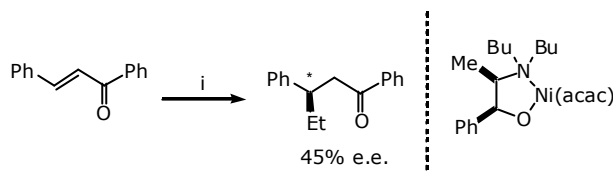
The first catalytic asymmetric 1,4-addition reaction was reported by Lippard in 1988.⁶¹ He disclosed the 1,4-addition of both phenyl and butyl magnesium chloride to cyclohexenone using a catalytic amount of a lithium copper-CHIRAMT complex to give the corresponding 1,4-addition products in excellent yields but more importantly with some stereochemical control, obtaining 4 and 14% e.e.'s, respectively (**Scheme 2.3.4.3**).



Reagents and Conditions: (i) 1.2 eq RMgCl, Li[Cu(CHIRAMT)], THF, -78 °C

Scheme 2.3.4.3 – Lippard's first asymmetric 1,4-addition using a copper-CHIRAMT system, 1988.

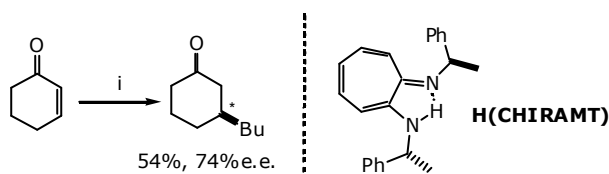
Soai, in the same year, reported the first catalytic 1,4-addition of dialkyl zinc reagents to aliphatic enone using a novel chiral nickel catalyst.⁶² Unfortunately, he found that the reaction required a substantial amount of catalyst to achieve only moderate selectivities, making the reaction too expensive to be synthetically viable (**Scheme 2.3.4.4**).



Reagents and Conditions: (i) 2.2 eq Et₂Zn, Ni cat (50 mol%), Tol, -30 °C

Scheme 2.3.4.4 – Soai's catalytic asymmetric 1,4-addition using a novel chiral nickel catalyst, 1988.

In 1990, Lippard published a modification of his asymmetric 1,4-addition reaction using the copper-CHIRAMT ligand system.⁶³ However this time using 1.5 eq. of the BuMgCl, TBDPSCI and HMPA he found he could obtain enantiomeric excesses up to 74% (**Scheme 2.3.4.5**).



Reagents and Conditions: (i) 1.5 eq BuMgCl, Ph₂(^tBu)SiCl [Cu(CHIRAMT)] (3 mol%), THF/HMPA, -78 °C

Scheme 2.3.4.5 – Lippard's modified asymmetric 1,4-addition using a copper-CHIRAMT system, 1990.

These early studies resulted in an explosion of research in the area largely examining various chiral ligands on the copper and nickel based catalysts to effect asymmetric transformations with both cyclohexenone and chalcone systems (**Figure 2.3.4.1**).⁶⁴⁻⁷¹

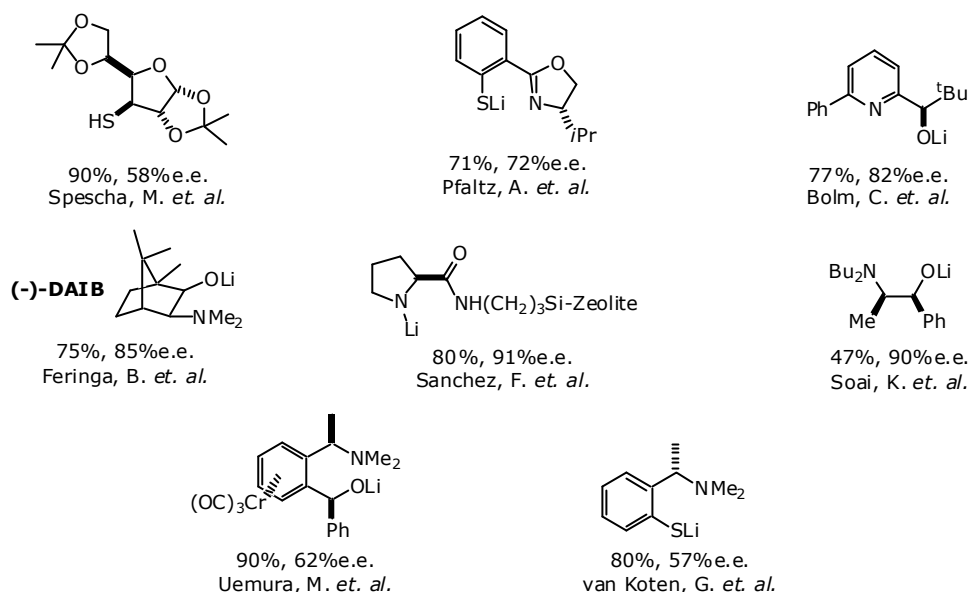
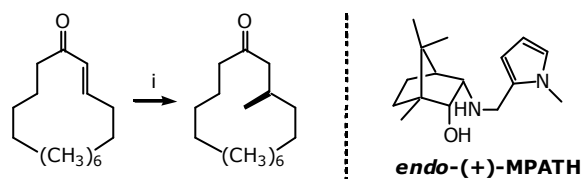


Figure 2.3.4.1 – Chiral ligands employed in asymmetric catalytic 1,4-addition reactions.

Catalytic asymmetric 1,4-addition methodology was later used in the synthesis of (*R*)-(-)-muscone. A copper-*endo*-(+)-MPATH ligand system promoted the required transformation in high yield and enantiomeric excess (**Scheme 2.3.4.6**).⁷²



Reagents and Conditions: (i) 1.7 eq MeLi, CuI (33 mol%), Ligand (36 mol%), 1.0 eq THF, Tol -78 °C, 3h

Scheme 2.3.4.6 – Tanaka's synthesis of (*R*)-(-)-muscone, 1993.

During the course of the aforementioned studies, several important observations were also made with regards to the structure of the copper complexes involved in these reactions. In particular, Koten isolated a copper trimer as a potential intermediate in the reaction (**Figure 2.3.4.2**).⁷³

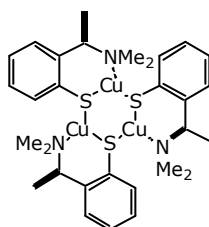


Figure 2.3.4.2 – A copper(III) intermediate isolated by van Koten, 1989.

Subsequent studies showed that electronic factors greatly influenced the outcome of these reactions relative to steric factors. The results also suggested that the

anchoring of the double bond to copper was probably more important for enantioselectivity than for the chemoselectivity in the reaction (**Figure 2.3.4.3**).⁷⁴

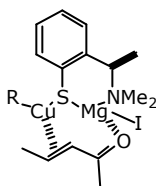
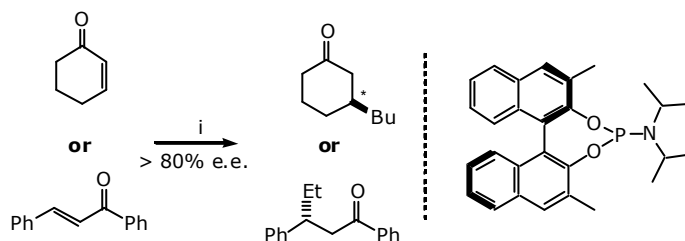


Figure 2.3.4.3 – Van Koten's proposed mode of complexation in his asymmetric 1,4-addition reactions, 1994.

In 1994 Pfaltz made some interesting observations with regards to the effects of additives on this type of reaction.⁷⁵ He found that the addition of both TMSCl and TBDPSCI resulted in lower selectivities whereas HMPA increased the yield of the reaction. Additionally, Grignard reagents with bromide counterions resulted in lower selectivities and yields relative to their chloride analogues.

Several more ligand systems were subsequently reported, specifically tailored for specific substrates; including chiral oxazoline-phosphites,⁷⁶ ferrocenyl phosphine oxazolines,⁷⁷ diphosphines,⁷⁸ phosphites,⁷⁹ TADDOLs,⁸⁰ bidentate phosphines,⁸¹ amidophosphines,⁸² and mixed O,S- and N, S-ligands.⁸³ All of these systems gave impressive yields and enantioselectivities for specific substrate systems.

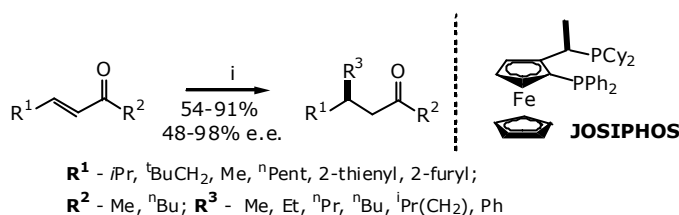
In 1996 Feringa introduced a novel catalytic system, using phosphorus amidite ligands on copper which revolutionised the area.⁸⁴ He reported the 1,4-addition of dialkyl zinc reagents to both aliphatic and cyclic enones catalysed by a copper triflate-phosphoramidite system in good yields and enantioselectivities (**Scheme 2.3.4.7**).



Reagents and Conditions: (i) 1.5 eq Et_2Zn or Bu_2Zn , CuOTf (3 mol%), ligand (4 mol%), Tol, -15°C

Scheme 2.3.4.7 – Feringa's phosphoramidite/copper catalysed 1,4-addition reaction, 1996.

Feringa later described the catalytic 1,4-addition of Grignard reagents to a wide range of unsaturated ketones using a copper-JOSIPHOS catalytic system (**Scheme 2.3.4.8**).^{85,86}

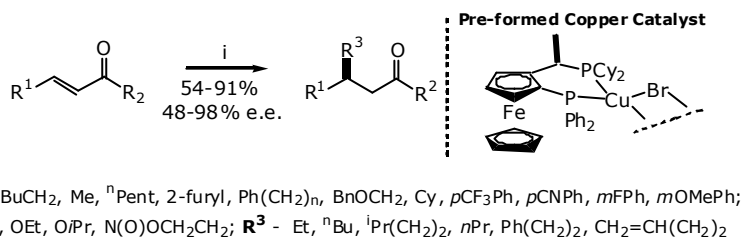


Reagents and Conditions: (i) 1.2 eq R^3 MgBr, CuBr.SMe₂ (5 mol%),
 Ligand (6 mol%), ^tBuOMe, -75 °C

Scheme 2.3.4.8 - Feringa's JOSIPHOS/copper catalysed 1,4-addition of Grignard reagents to enones, 2004.

The reaction proceeded with good to exceptional enantioselectivities and proved to be of wide scope with regards to substrate, although aryl Grignard reagents continued to be more problematic.

Recently, Feringa reported the catalytic 1,4-addition of Grignard reagents to unsaturated esters, once again using the copper-JOSIPHOS catalytic system. However this time the catalyst complex was pre-formed and shown to be bench stable (**Scheme 2.3.4.9**).⁸⁷



Reagents and Conditions: (i) 1.2 eq R^3 MgBr, copper catalyst (3 mol%), ^tBuOMe, -75 °C

Scheme 2.3.4.9 - Feringa's pre-formed copper catalysed 1,4-addition, 2005.

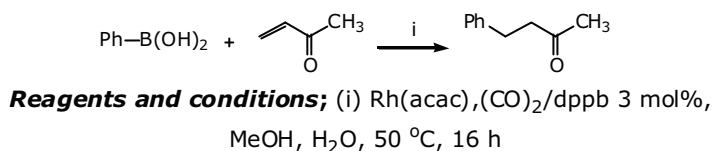
A wide range of unsaturated substrates were shown to be compatible with the reaction, although again aryl Grignard reagents were conspicuously absent.

2.4 Rhodium Catalysed 1,4-Addition Reactions

In parallel with the above developments, there has been great interest in the use of rhodium complexes as catalysts for the 1,4-addition of aryl and vinyl boronic acids and related organometals to Michael acceptors. This methodology has attracted attention by synthetic chemists both because of its complementarity to the copper-based approaches, for which aryl transfer is difficult, and because of the high tolerance of the rhodium systems to oxygen and moisture. From an environmental perspective, rhodium is a relatively 'green' transition metal

because it forms highly stable complexes which allows many reactions to occur in aqueous solvent systems.⁸⁸

In 1997, Miyaura reported the first 1,4-addition of an organoboronic acid to an enone catalysed by a rhodium complex:⁸⁹ the addition of phenyl boronic acid to methyl vinyl ketone (**Scheme 2.5.1**).



Scheme 2.4.1 – Miyaura's first reported rhodium-catalysed 1,4-addition reaction, 1997.

Miyaura used Rh(acac)(CO)₂ as the catalyst precursor and dppb as the phosphine ligand, in an aqueous solvent system at 50 °C for 16 h, to afford the product in 99% yield.

Hayashi later described how this new rhodium catalysed reaction provided several advantages over previously reported methods:⁹⁰

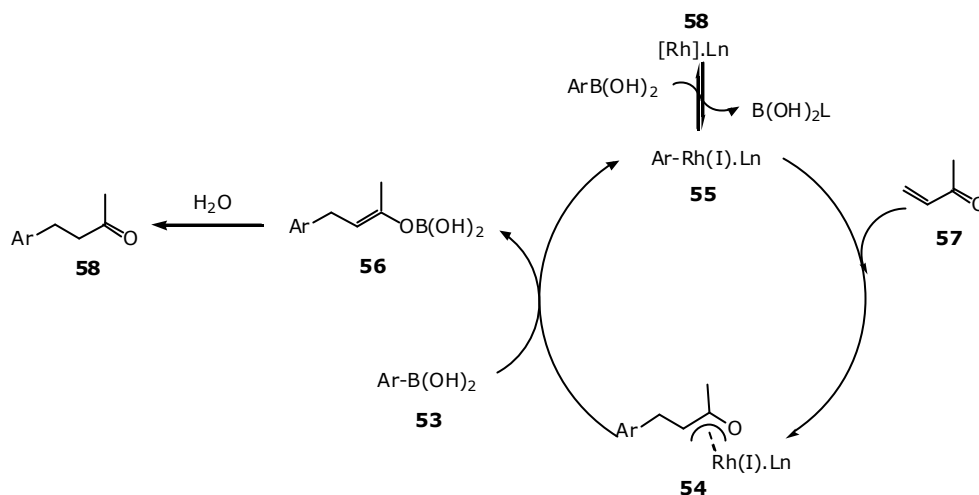
- Organoboronic acids are oxygen and moisture stable,
- The reaction takes place in protic or even aqueous media,
- The reaction proceeds to give the 1,4-addition product only, with no competing 1,2-addition,
- The reaction is particularly successful for aryl and alkenyl boronic acids.
- In the absence of the rhodium complex, the boronic acids are much less reactive towards enones; a pre-requisite for efficient asymmetric variants.

Hayashi reported an asymmetric modification in the same report.⁹⁰ In order to achieve enantioselectivity in this reaction, he made several changes to the reaction conditions now using Rh(acac)(C₂H₄)₂/(S)-BINAP as the catalyst and aqueous dioxane as the solvent system, at 100 °C. These modifications have been referred to as the *standard conditions* for a rhodium catalysed asymmetric 1,4-addition reaction.⁹⁰

Since this initial report many groups have explored this reaction. The following section discusses some of the proposed catalytic cycles and the associated supporting evidence.

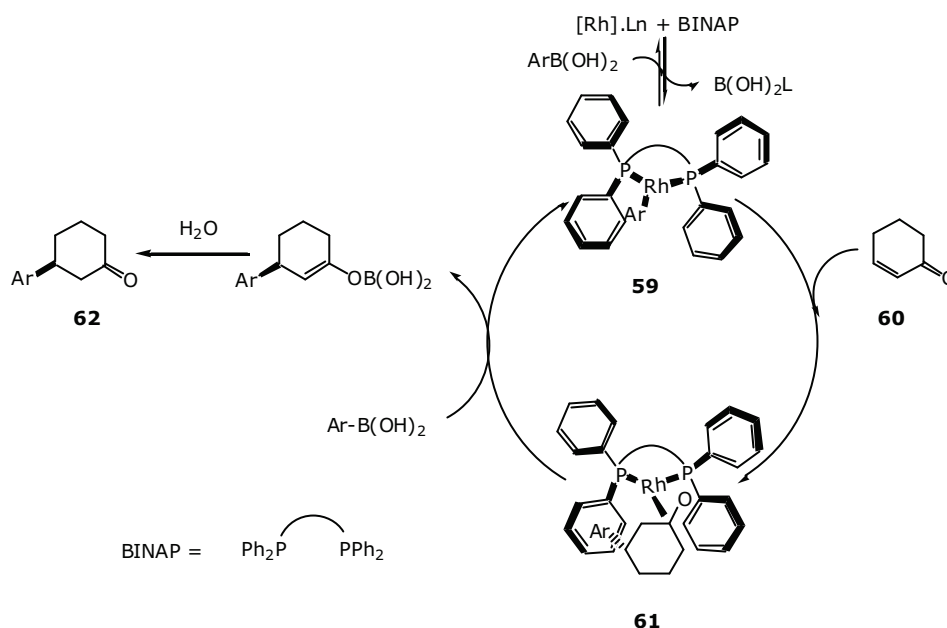
2.4.1 Reaction Mechanism

Miyuara proposed a catalytic cycle in which he speculated that the key step involved the transmetalation of an aryl group from the boronic acid **53** to an aryl Rh(I) species **55** which underwent the 1,4-addition reaction to give a Rh(I) enolate **54**. This enolate then participates in the next cycle of transmetalation with concomitant formation of the corresponding boron enolate **56**. Hydrolysis of this boron enolate **56** gave rise to the final product **58** (Scheme 2.4.1.1).⁸⁹



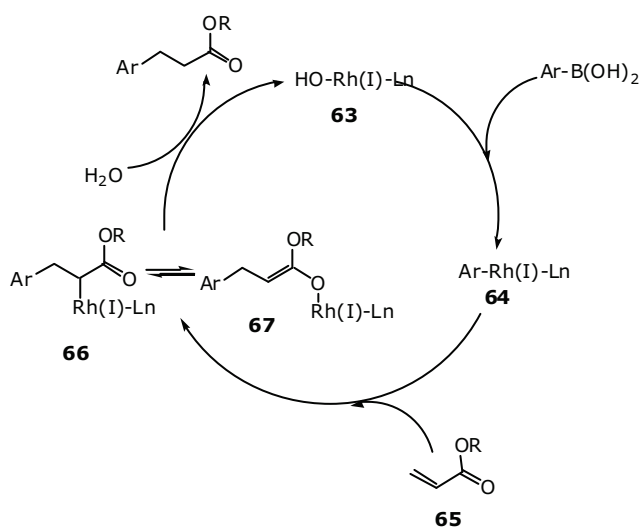
Scheme 2.4.1.1- Miyuara's proposed catalytic cycle for 1,4-addition of arylboronic acids to enones, 1997.

Following this Hayashi described the enantioselective rhodium catalysed 1,4-addition using (*S*)-BINAP as a chiral ligand on rhodium complex **59** to effect asymmetric induction in the reaction.⁹⁰ Selectivity was achieved by blocking one of the two vacant sites on the key aryl Rh(I) complex by a phenyl ring on the (*S*)-BINAP ligand, therefore only allowing access from the opposite face. The coordination of enone **60** to the rhodium complex **59** occurs *via* its *2*si**-face as in complex **61** leading *via* migratory insertion to an *S* configured product **62** (Scheme 2.4.1.2).



Scheme 2.4.1.2 - Hayashi's proposed catalytic cycle for asymmetric 1,4-addition of aryl boronic acids to enones reaction using (S)-BINAP as the chiral ligand, 2000.

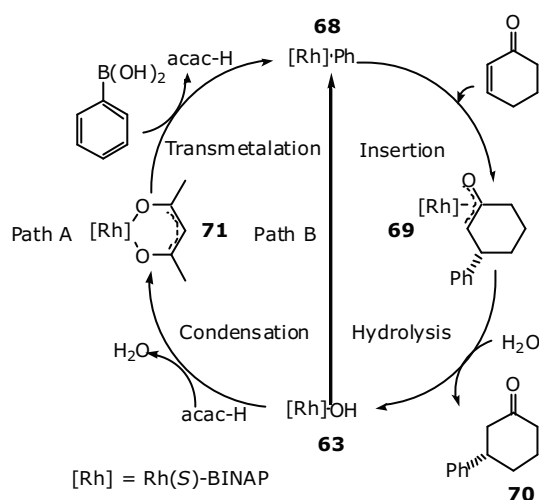
Miyaura later argued that the reaction mechanism involved a hydroxyrhodium(I) species **63**; which provided some explanation as to why H_2O was pre-requisite for the reaction to work.⁹¹ He claimed, that it was this rhodium complex that actively received an aryl group through transmetalation from the boronic acid, to yield the arylrhodium species **64**. 1,4-addition of the aryl group at the β -carbon of the α,β -unsaturated substrate **65** gave a Rh(I) enolate which exists as an equilibrium between the C-Rh and O-Rh (**66** and **67**). After hydrolysis, the product was released and the hydroxyrhodium(I) species **63** was regenerated (**Scheme 2.4.1.3**).⁹¹



Scheme 2.4.1.3 - Miyaura's revised catalytic cycle for 1,4-addition of arylboronic acid to enones involving the participation of a hydroxyrhodium(I) species **63**, 2000.

It soon became apparent, that H_2O played a vital role in the catalytic cycle. In particular, it prevented β -hydride elimination occurring, which would normally afford the Heck or the aldol condensation product, which are not observed in these reactions. Several authors also reported that the reaction did not proceed efficiently in the absence of H_2O .^{88,92}

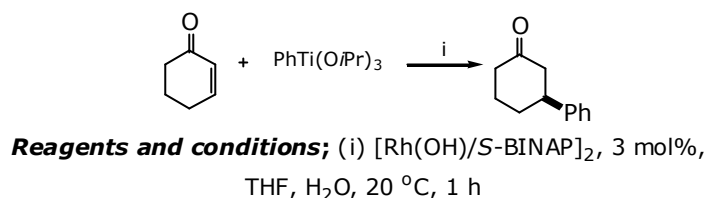
It was later in 2002 that Hayashi clearly established the mechanism for the rhodium-catalysed asymmetric 1,4-addition of organoboronic acids to enones.⁹³ He derived the catalytic cycle by conducting ^1H and ^{31}P NMR studies. Through these studies three key intermediates were observed; a phenyl rhodium complex **68**, a rhodium enolate **69** and finally a hydroxyrhodium complex **63**, which had been previously predicted by Miyaura (**Scheme 2.4.1.4**).



Scheme 2.4.1.4-Hayashi's proposed catalytic cycle for 1,4-addition of aryl boronic acids to enones 2002.

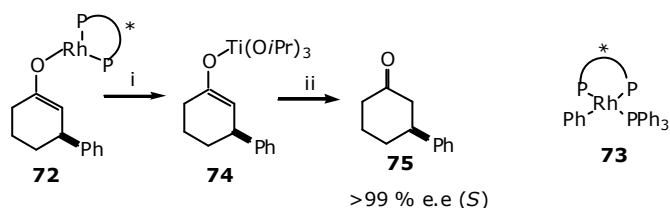
From the results of these studies Hayashi postulated that an aryl rhodium complex **68** first undergoes a 1,4-addition to the enone. The aryl group then attacks the β -carbon stereoselectively, under the control of the chiral ligands on the rhodium and the rhodium complex becomes part of a rhodium enolate species **69**. The loss of H_2O then releases the desired product **70** and a hydroxyrhodium complex **63**. Using the conventional $\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2/(\text{S})\text{-BINAP}$ catalyst, the cycle follows pathway A, where 'acac' provides a proton for the condensation of the hydroxyrhodium complex **63** to form the catalytic precursor **71**. The aryl group on the boronic acid then undergoes transmetalation with catalytic precursor **71** to form the active aryl rhodium complex **68**. Alternatively, Hayashi found that an aryl boronic acid could transmetalate to the hydroxyrhodium(I) complex **63** to form the active catalyst **68** directly *via* pathway B. The new hydroxyrhodium(I)

catalyst **63** was shown to be more effective than the conventional $\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2/(S)\text{-BINAP}$ catalytic system. This difference was exemplified in organotitanium rhodium-catalysed 1,4-addition reactions.⁹⁴ The 1,4-addition of phenyltitanium triisopropoxide to cyclohexenone, using $[\text{Rh}(\text{OH})/(S)\text{-BINAP}]_2$ complex as catalyst yielded the 1,4-addition product in 85% yield and 99.5% enantiomeric excess (**Scheme 2.4.1.5**).



Scheme 2.4.1.5 - Hayashi's enantioselective 1,4-addition of $\text{PhTi}(\text{O}i\text{Pr})_3$ to cyclohexenone, 2002.

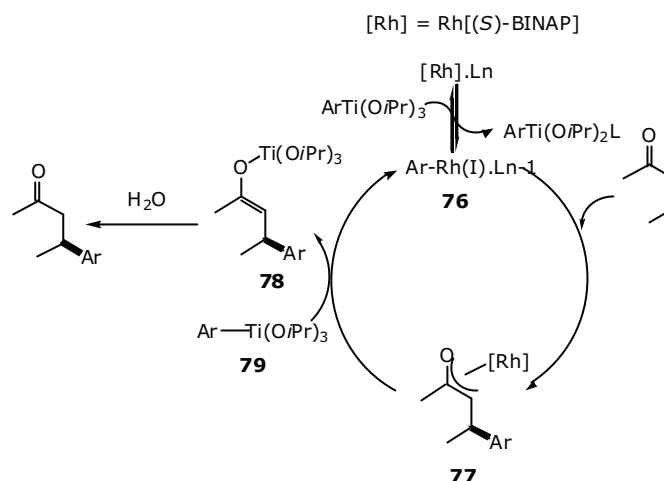
^{31}P NMR studies showed that the stoichiometric addition of the phenyl organotitanium reagent to the rhodium enolate (*S*)-BINAP derived complex **72**, in the presence of triphenylphosphine in THF, generated two products: the phenylrhodium complex **73**, coordinated to (*S*)-BINAP and triphenylphosphine, and the titanium enolate of the 1,4-addition product **74** which on hydrolysis gave ketone **75** in >99% e.e. (**Scheme 2.4.1.6**).



Reagents and conditions; (i) $\text{PhTi}(\text{O}i\text{Pr})_3$, PPh_3 , THF; (ii) MeOH

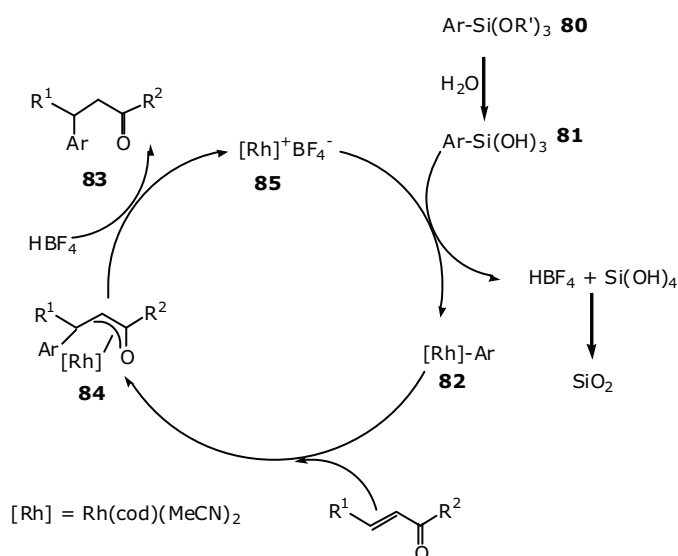
Scheme 2.4.1.6 - Intermediates in the asymmetric 1,4-addition of triisopropoxyphenyl titanium to cyclohexenone as verified by ^{31}P NMR by Hayashi, 2002.

This suggested a catalytic cycle involving a two-step mechanism. The first step involves the insertion of the enone into the arylrhodium complex, thereby forming the rhodium enolate **76**. The second step is the transmetalation of the enolate from this the rhodium complex **77** to give the corresponding titanium enolate **78** by reaction with aryl titanium **79** with concomitant reformation of arylrhodium complex **76** (**Scheme 2.4.1.7**).



Scheme 2.4.1.7- Hayashi's proposed catalytic cycle for 1,4-addition of aryltitanium reagents to enones, 2002.

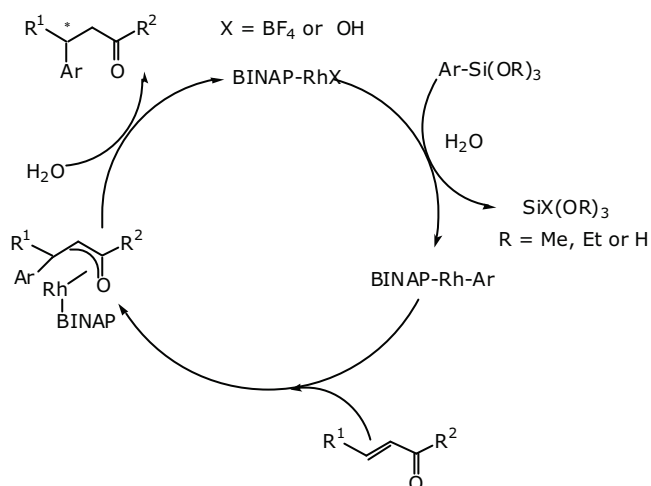
Oi reported the 1,4-addition reaction between organosiloxanes and α,β -unsaturated carbonyl compounds,⁹⁵ using $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{BF}_4$ as the catalyst. He, like many others, reported that H_2O was essential for the reaction to occur, but defined a different role for H_2O in the catalytic cycle to that postulated previously (**Scheme 2.4.1.8**).



Scheme 2.4.1.8 - Oi's proposed catalytic cycle for 1,4-addition of arylsiloxanes to enones, 2002.

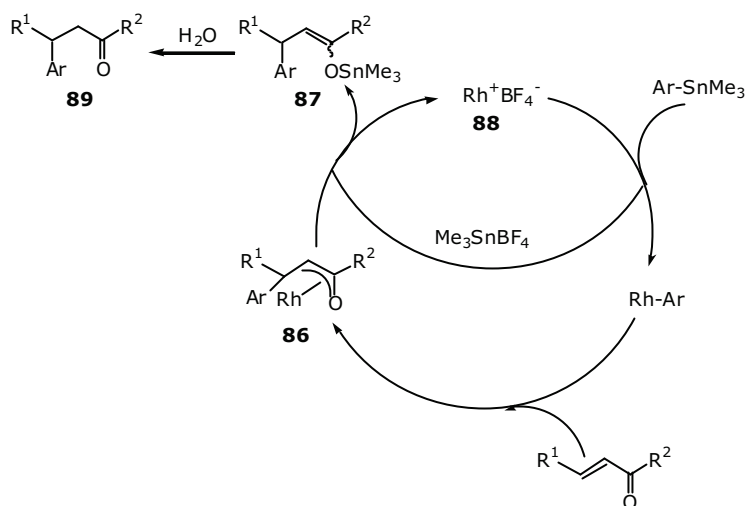
Oi proposed a catalytic cycle in which the role of H_2O was to mediate the hydrolysis of the organosiloxane **80** to organosilanol **81**. The organosilanol species **81** then enters the catalytic cycle by transmetalation of the aryl group to the rhodium tetrafluoroborate salt to give the arylrhodium complex **82**. The remainder of the cycle is as previously described, with the exception of the final step. For the final step, he speculated that the desired product **83** was liberated

from the rhodium intermediate **84** by HBF_4 , thereby regenerating the rhodium complex **85**, (water had previously been suggested to play this role in the cycle, leading to the formation of the hydroxyrhodium complex observed in the analogous reaction with organoboronic acid reagents). Oi, later described the asymmetric version of this reaction using a BINAP ligand on rhodium,⁹⁶ proposing a similar catalytic cycle to the non-asymmetric version except that in this cycle he did invoke H_2O as the reprotonating species (**Scheme 2.4.1.9**).⁹³



Scheme 2.4.1.9 - Oi's proposed catalytic cycle for asymmetric 1,4-addition of organosiloxanes to enones, 2003.

Oi also reported the 1,4-addition reaction of organostannane reagents with α,β -unsaturated carbonyl compounds.⁹⁷ He found that the addition of methanol or H_2O to the reaction mixture significantly increased the yields, but that the addition of acetic acid did not show similar enhancements. Consequently, Oi proposed a similar catalytic cycle to that which he proposed for the non-asymmetric organosiloxane addition process, only differing in that the role of H_2O was redefined again (**Scheme 2.4.1.10**).



Scheme 2.4.1.10 - Oi's proposed catalytic cycle for 1,4-addition of arylstannanes to enones, 2002.

In this cycle the Me₃SnBF₄ complex formed as a by-product of the transmetalation of the aryl group from the tin to the rhodium in the first step, is later involved in transmetalation of the enolate from the rhodium complex **86**, to form an organostannane enolate **87** and the regeneration of the rhodium salt **88**. H₂O then hydrolyses the newly formed stannyl enolate **87** to afford the enone product **89**. NMR studies of the reaction mixture in the absence of H₂O indicated the formation of the stannyl enolate **87**. This supported the idea that H₂O was not a key player in the catalytic cycle itself, but played a secondary role by hydrolysing the stannyl enol ether to afford the product.

Further NMR studies on the reaction using stoichiometric Rh(cod)(MeCN)₂]BF₄ and phenyl trimethylstannane in D₂O and THF at ambient temperature for 20 h, showed that the stannane species had been completely converted to d₁-benzene. A control experiment between trimethylstannane and H₂O in the absence of the rhodium complex showed that the stannane species was inert to H₂O. On the basis of these observations it was proposed that transmetalation of the aryl group between the arylstannane species and the rhodium complex occurs to yield an arylrhodium intermediate. This intermediate then quickly reacts with the enone to form the rhodium enolate. If the enone is too hindered or not present at all, the rhodium complex will proceed to react with the H₂O present in the reaction to demetalate. This implies that the rate of reaction between the arylrhodium complex and the enone is faster than the reaction between the arylrhodium complex and H₂O. The exception is when the enone is significantly hindered at the β-carbon in which the case the rate of the reaction is sufficiently reduced that the competing

reaction with H₂O takes place preferentially, leading to the decomposition of the active rhodium species.

From the foregoing survey it is clear that there has been much deliberation regarding the reaction mechanism of rhodium catalysed 1,4-addition reactions. Hayashi has unequivocally elucidated, by means of ¹H NMR studies, the main features of the catalytic cycle for asymmetric 1,4-addition reactions of arylboronic acids to enones. Although several other mechanisms have been postulated for related reactions involving reagents other than boronic acids, all agree on two keys steps. First, that the aryl group undergoes transmetalation to afford an arylrhodium complex, which is the active species in this reaction; secondly, that the reaction proceeds to form a rhodium enolate intermediate by 1,4-addition of this species to the enone. The involvement of H₂O in these reactions, however, is still being debated, although there is a general consensus that it does play a vital role in the catalytic cycle.

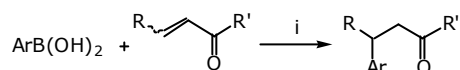
From a synthetic perspective, and irrespective of the detailed mechanism, rhodium catalysed 1,4-addition reactions have received considerable attention in recent years, and have inspired many synthetic chemists to further develop this methodology for a wide range of substrates and reagents. There have been two comprehensive reviews published in this area,^{88,98} which detail much of the work done so far with regards to substrate, reagents and conditions. In view of this, the following section reviews the literature specifically related to the application of this methodology to our proposed natural product synthesis of hydroxy *iso*-evoninic acid.

To this end there are several factors that need to be considered in order to effectively apply this methodology. First, there have been no examples in the literature of pyridyl metal reagents and few examples of electron deficient aryl metal reagents undergoing 1,4-addition reactions with α,β -unsaturated carbonyl compounds catalysed by a rhodium complex. Therefore it was anticipated at the start of the project that it would be necessary to prepare and evaluate various 4-metallo pyridines as potential partners in the envisioned rhodium catalysed 1,4-addition reactions. Second, there are very few examples of *ortho*-substituted aryl metal species undergoing rhodium catalysed 1,4-addition. Therefore, it was anticipated that it would also be necessary to evaluate the feasibility of carrying such substituents through this type of the reaction. Literature examples where the sterically congested aryl metals have successfully undergone 1,4-addition

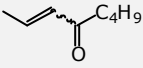
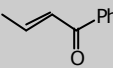
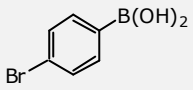
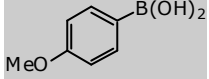
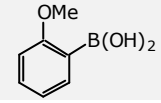
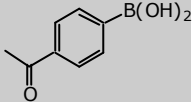
reactions are highlighted in the following survey. Third, disubstituted α,β -unsaturated esters, substituted at the α - and β -positions have rarely been studied as substrates and so the feasibility of using this type of substrate would also need to be evaluated; particularly examples containing methyl tiglate or angelate. Fourth, an asymmetric variant of the reaction would be desirable. Consequently, factors affecting the success of asymmetric 1,4-addition reactions are highlighted below.

2.4.2 Summary of the Literature

In Miyaoura's initial publication on the rhodium-catalysed 1,4-addition reaction of arylboronic acids with enones, a number of enones and boronic acids were investigated (**Table 2.4.2.1**).⁸⁹



Reagents and conditions; (i) Rh(acac)(CO)₂, 3 mol%,
aq. solvent, 100 °C, 16 h

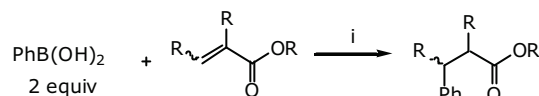
Entry	Enone	ArB(OH) ₂	DMF/H ₂ O Yield/%	Cyclohexane/H ₂ O Yield/%	MeOH/H ₂ O Yield/%
1		PhB(OH) ₂	28	60 74 ^a	96 ^a
2		PhB(OH) ₂	----	75 ^a	----
3		PhB(OH) ₂	82	90	99
4		PhB(OH) ₂	----	43 ^a	----
5			90	----	----
6			84	82	86
7			68	81	84
8			94	----	----

^a 2 equivalents of boronic acid used

Table 2.4.2.1⁸⁹ – Miyaura's 1,4-addition reactions between arylboronic acids and enones, 1997.

Miyaura described a promising observation with regards to our synthetic strategy with the addition of *ortho*-methoxyphenylboronic acid, to methyl vinyl ketone (**Table 2.4.2.1, entry 7**). This reaction proceeds in high yields using a variety of aqueous solvent systems with an aqueous methanol solvent system seemingly providing the best results. Examples of electron deficient systems undergoing 1,4-addition reactions are also described (**Table 2.4.2.1, entries 5 & 8**). However, these reactions were only shown to proceed when using DMF/H₂O as the solvent system. Miyaura noted that there was no appreciable difference in efficiency between electron-withdrawing or electron-donating groups on the phenyl ring. However, he claimed that *ortho*-substituents strongly retarded the addition step, and therefore suggested that an excess of boronic acid, with respect to enone, was advantageous to achieve high yields for these substrates.

In 2000, Miyuara reported the 1,4-addition reaction of arylboronic acids to α,β -unsaturated esters (**Table 2.4.2.2**).⁹¹



Reagents and conditions; (i) Rh(acac)(C₂H₄)₂, 3 mol%

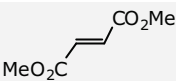
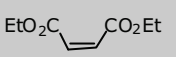
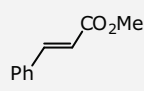
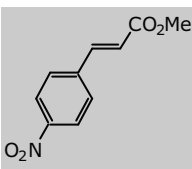
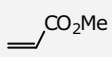
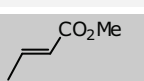
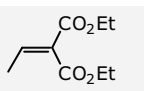
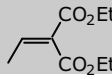
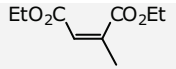
Entry	Substrate	Temp °C	Solvent (Solvent/H ₂ O)	Yield/%	Reaction Time
1		25	aq. MeOH (6/1)	84	16h
2		25	aq. MeOH (6/1)	79	16h
3		50	aq. MeOH (6/1)	87	16h
4		50	aq. MeOH (6/1)	97	16h
5		80	aq. dioxane (6/1)	60	----
6		100	aq. dioxane (6/1)	82	16h
7		100	aq. dioxane (6/1)	9	16h
8		70	aq. EtOH	76	24h
9		100	aq. dioxane	trace	16h

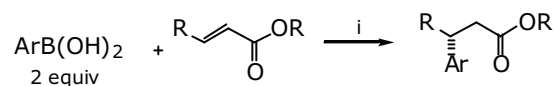
Table 2.4.2.2⁹¹ – Miyuara's 1,4-addition reactions between arylboronic acids and α,β -unsaturated esters, 2000.

These results are particularly pertinent to our work, as our strategy involves the 1,4-addition reaction between an aryl metal derivative and an α,β -unsaturated ester. Of particular interest are the 1,4-addition reactions of trisubstituted α,β -unsaturated esters (**Table 2.4.2.2, entries 7 and 8**). The reactions are highly dependent on the reaction conditions, particularly the solvent system. The reaction between the trisubstituted α,β -unsaturated ester conducted in aqueous dioxane at 100 °C gave the desired product in very low yield (**Table 2.4.2.2, entry 7**). However, if the solvent was changed to aqueous ethanol, the reaction proceeded to afford the desired product in good yield (**Table 2.4.2.2, entry 8**).

Overall, the data for the 1,4-addition between arylboronic acids and α,β -unsaturated esters are very promising.

In 1998, Hayashi reported an asymmetric variant of the 1,4-addition reaction between arylboronic acids and α,β -unsaturated esters (**Table 2.4.2.3**).^{90,91}

The most interesting feature of this data is that all the reactions proceed with high enantioselectivities (88-98 %). (*S*)-BINAP was used as the chiral ligand on rhodium complex, along with the 'standard conditions' determined for the asymmetric 1,4-addition reactions with enones previously described.⁹⁰ Only β -substituted- α,β -unsaturated esters were investigated in conjunction with various arylboronic acids. Of particular interest are the reactions that involve *ortho*-substituted arylboronic acids (**Table 2.4.2.3, entries 10 and 11**). These reactions proceed in moderate to low yield, 35 and 43% respectively, but in exceptionally high enantioselectivities (94% and 98% e.e. respectively).



Reagents and conditions; (i) Rh(acac)(C₂H₄)₂, 3 mol%, (S)-BINAP, aq. dioxane, 100 °C, 16 h

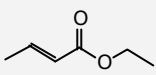
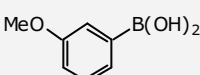
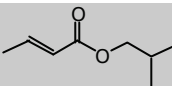
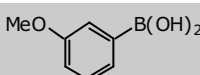
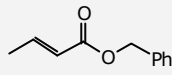
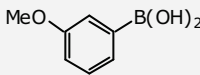
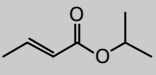
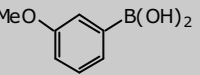
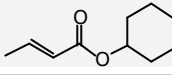
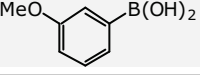
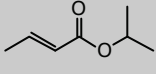
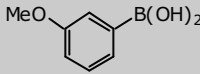
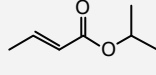
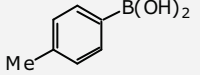
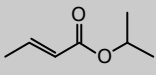
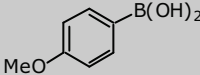
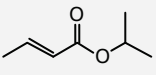
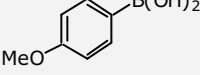
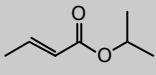
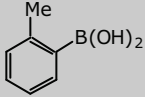
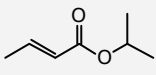
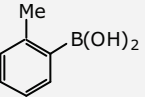
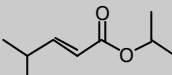
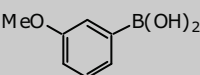
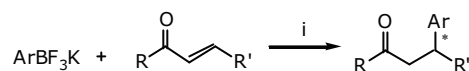
Entry	Substrate	ArB(OH) ₂	Yield/% (e.e./%)
1			81(87)
2			98(88)
3			97(87)
4			91(91)
5			97(91)
6			54(92)
7			89(92)
8			55(92)
9		 5 equiv	82(92)
10		 5 equiv	35(94)
11		 5 equiv	43(98)
12			26(97)

Table 2.4.2.3^{90,91} – Hayashi's asymmetric 1,4-addition reactions between arylboronic acids and α,β -unsaturated esters, 1998.

In 2002, Genet described the use of potassium aryltrifluoroborates as partners in enantioselective 1,4-addition reactions with enones (**Table 2.4.2.4**).⁹⁹



Reagents and conditions; (i) Rh(cod)PF₆, 3 mol%, (S)-BINAP, H₂O:Tol (1:4), 100 °C, 1 h

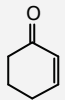
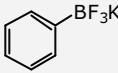
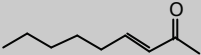
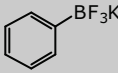
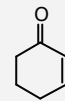
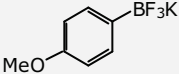
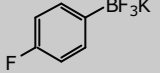
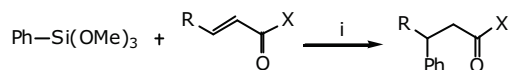
Entry	Substrate	ArBF ₃ K	Time	Yield/% (e.e./%)
1			1h	99(98)
2			1h	99(92)
3			6h	97(90)
4			2h	95(98)

Table 2.4.2.4⁹⁹ – Genet's asymmetric 1,4-addition reactions between potassium aryltrifluoroborates and enones, 2002.

The potassium aryltrifluoroborates are highly resistant to deboronation relative to their boronic acid analogues as the result of being hyper-valent.¹⁰⁰ Electron-deficient aryl reagent *p*-FC₆H₄BF₃K was shown to successfully undergo 1,4-addition under these conditions to give the desired product in 95% yield and 98% e.e. (**Table 2.4.2.4, entry 4**).

In 2002, Oi described the reaction of arylsiloxanes with various α,β -unsaturated carbonyl compounds.⁹⁵ He primarily focused on enones but highlighted that other substrates such as α,β -unsaturated esters and nitriles were equally successful in these reactions (**Table 2.4.2.5**).



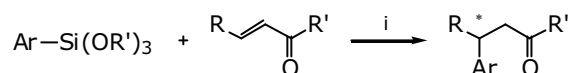
Reagents and conditions; (i) [Rh(cod)(MeCN)₂]BF₄, 2 mol%,
H₂O:dioxane (1:10), 90 °C, 20 h

Entry	Substrate	Yield/%
1		93
2		79
3		90
4		73
5		97
6		82

Table 2.4.2.5⁹⁵ – Oi's 1,4-addition reaction between arylsiloxanes and α,β -unsaturated carbonyl compounds, 2002.

A new rhodium catalyst, [Rh(cod)(MeCN)₂]BF₄ was used in these reactions. This catalyst has subsequently proved to be a valuable addition to the repertoire of catalysts suitable for these reactions. Oi showed that the reaction between phenyl trimethylsiloxanes and *trans*-methyl cinnamates proceeded in particularly high yield (**Table 2.4.2.5, entry 5**).

Oi later published an asymmetric version of the above reaction,⁹⁶ using (*S*)-BINAP as the chiral ligand and enones as substrates (**Table 2.4.2.6**).



Reagents and conditions; (i) $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{BF}_4$, 4 mol%, (S)-BINAP
 H_2O :dioxane (1:10), 90 °C, 20 h

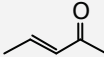
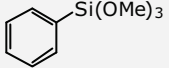
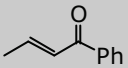
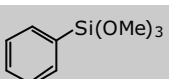
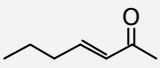
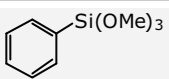
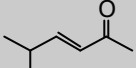
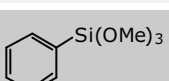
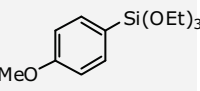
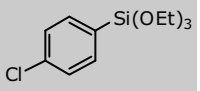
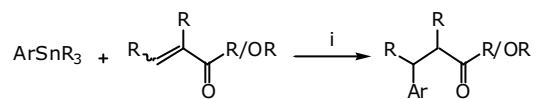
Entry	Substrate	ArSi(OMe) ₃	Yield/% (e.e./%)
1			90(75)(R)
2			90(75)(R)
3			87(91)
4			62(98)
5			73(96)
6			56(96)

Table 2.4.2.6⁹⁶ - Oi's asymmetric 1,4-addition reaction between arylsiloxanes and α,β -unsaturated carbonyl compounds, 2003.

Of note is the reaction between $p\text{-ClC}_6\text{H}_4\text{Si}(\text{OMe})_3$, an electron deficient arylsiloxane, and 2-cyclohexenone that affords the product in moderate yield (56%), but in high e.e. (96%) (**Table 2.4.2.6, entry 6**).

In 2002, Oi showed that arylstannanes also participate in this type of reaction.⁹⁷ Arylstannanes are attractive alternatives to arylboronic acids because not only do they undergo 1,4-addition reactions with α,β -unsaturated esters (**Table 2.4.2.6, entries 9-13**), but because aryl stannanes are much more resistant to destannylation than boronic acids and esters are to deboronation. This was particularly attractive considering the known instability of 4-pyridylboronic acids to deboronation under aqueous conditions (**Table 2.4.2.7**).



Reagents and conditions; (i) $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{BF}_4$, 2 mol%,
THF, 60 °C

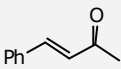
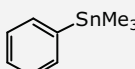
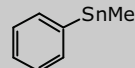
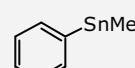
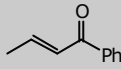
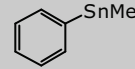
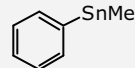
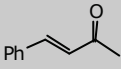
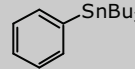
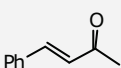
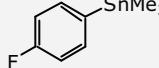
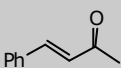
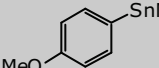
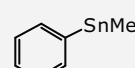
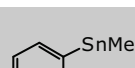
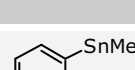
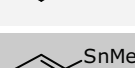
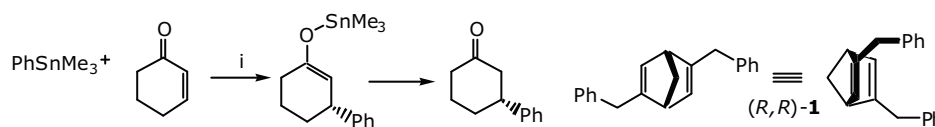
Entry	Substrate	ArSnR ₃	Time/h	Yield/%
1			2	98
2			5	80
3			5	88
4			2	60
5			24	37
6			2	70
7			2	68
8			2	74
9			2	66
10			2	75
11			2	71
12			2	90
13			2	----

Table 2.4.2.7⁹⁷ - Oi's 1,4-addition reaction between arylstannanes and α,β -unsaturated carbonyl compounds, 2002.

Electron-deficient arylstannane $p\text{-FC}_6\text{H}_4\text{SnMe}_3$ was shown to undergo 1,4-addition reactions with an enone in moderate yield (**Table 2.4.2.7, entry 7**). A number

of α,β -unsaturated esters also participated in 1,4-addition reactions with arylstannanes in moderate to high yields (**Table 2.4.2.7, entries 9-12**). Particularly interesting was the reaction of an α -methyl substituted α,β -unsaturated ester (**Table 2.4.2.7, entry 10**). Less encouraging was the unsuccessful reaction of methyl tiglate with phenyl trimethylstannane (**Table 2.4.2.7, entry 13**). As previously described (see **2.4.1 Reaction Mechanism**), NMR studies showed that for hindered substrates the competing reaction of the aryl-rhodium intermediate with H_2O becomes dominant resulting in the decomposition of the active rhodium complex.

The asymmetric reaction of arylstannanes using (*S*)-BINAP as a chiral ligand on rhodium has also been investigated. The results obtained suggested that the 1,4-addition reaction was severely hindered by the phosphine ligand to the extent that some reactions did not proceed at all.⁹⁷ Hayashi later demonstrated that a phosphine-free chiral chelating diene (*R,R*)-**1**, could be used to induce asymmetry in these reactions, obtaining the 1,4-addition product in 80% yield and 95% e.e. (**Scheme 2.4.2.1**).^{101,102}

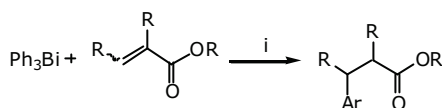


Reagents and conditions; (i) $[\text{RhCl}(\text{C}_2\text{H}_4)_2]/(R,R)\text{-1}$, 3 mol%,
NaOMe (6 mol%), Tol, 60 °C, 22 h

Scheme 2.4.2.1 - Hayashi's asymmetric rhodium-catalysed 1,4-addition reaction with arylstannanes, 2003.

The use of organobismuth reagents in rhodium catalysed 1,4-addition reactions, has also been reported recently by Li.¹⁰³ He reported that the reaction between triphenylbismuth and α,β -unsaturated esters and ketones in an aqueous medium and in open flasks gave the corresponding 1,4-addition products in high yields (**Table 2.4.2.8**).

It can be seen that α,β -unsaturated esters generally work well in this reaction, but the yields obtained are highly dependent on the level of substitution. For example, the acrylate ester (**Table 2.4.2.8, entry 1**) gives just 11% yield with triphenylbismuth, whereas the crotonate ester and α -methyl acrylate esters (**Table 2.4.2.8, entries 2 & 3**) give good yields. No asymmetric version of this reaction has been described.



Reagents and conditions; (i) $[\text{Rh}(\text{cod})_2]\text{BF}_4/\text{Rh}(\text{cod})_2\text{Cl}_2$, 5 mol%, THF/H₂O, 50 °C, 12 h, air

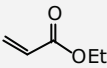
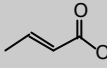
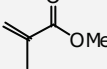
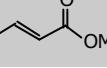
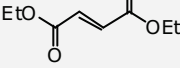
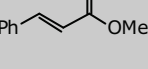
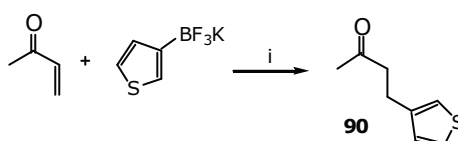
Entry	Substrate	Yield/%
1		11
2		80
3		70
4		80
5		74
6		68

Table 2.4.2.8¹⁰³ – Li's 1,4-addition reactions between organobismuth reagents and α,β -unsaturated esters, 2001.

Particularly pertinent to our strategy, in 1999 Batey reported the first 1,4-addition of a heteroaryl boron reagent participating in a 1,4-addition reaction to an enone (**Scheme 2.4.2.2**).¹⁰⁴

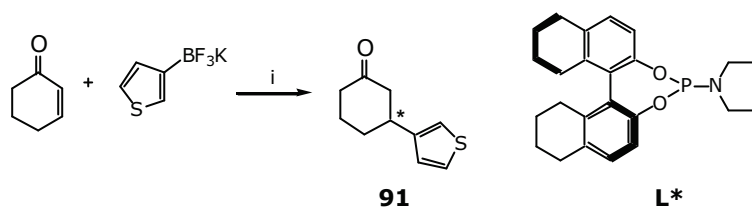


Reagents and conditions; (i) $\text{Rh}(\text{acac})(\text{CO})_2$, 3 mol%, dppb 3 mol %, MeOH/H₂O, reflux

Scheme 2.4.2.2– Batey's 1,4-addition of 3-thiophene trifluoroborate potassium salt to an enone.

A single example of a potassium 3-thiophene trifluoroborate reagent was added to an enone to give the desired product, ketone **90** in quantitative yield. This to the best of our knowledge this is the first example of a heteroaromatic reagent undergoing this reaction.

In 2004, Feringa described the enantioselective addition of the same reagent (potassium 3-thiophene trifluoroborate) to cyclohexenone with the aid of a phosphoramidite ligand **L*** (**Scheme 2.4.2.3**).¹⁰⁵

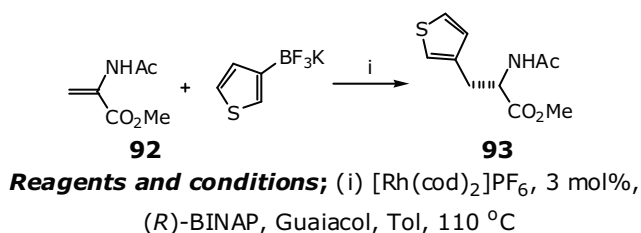


Reagents and conditions; (i) Rh(acac)(eth)₂, 4 mol%,
Ligand **L***, EtOH, reflux, 2 h

Scheme 2.4.2.3 – Feringa's 1,4-addition of 3-thiophene trifluoroborate potassium salt to cyclohexenone.

The reaction proceeded to give the desired product, ketone **91** in moderate yield (68%), but in excellent enantiomeric excess (99% e.e.).

Genet subsequently reported the enantioselective 1,4-addition of the same potassium trifluoroborate reagent to an α,β -unsaturated ester **92** (**Scheme 2.4.2.4**).¹⁰⁶



Scheme 2.4.2.4 – Genet's 1,4-addition of 3-thiophene trifluoroborate potassium salt to an unsaturated ester.

With the aid of a (*R*)-BINAP ligand on the rhodium complex, the reaction proceeded to give the desired product ester **93** in moderate yield (68%), and in good enantiomeric excess (81% e.e.).

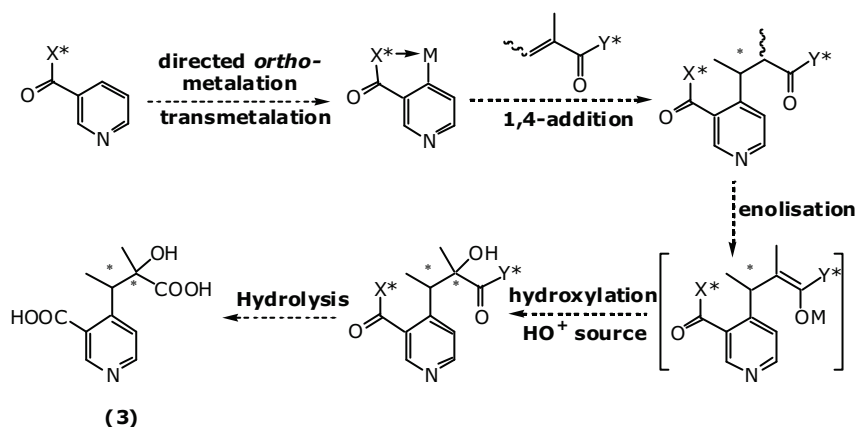
It is clear from the foregoing survey that there is limited precedent for *ortho*-substituted and electron deficient aryl metals successfully participating in rhodium catalysed 1,4-addition reactions. There are also a limited number of examples where α,β -disubstituted- α,β -unsaturated esters having successfully undergone these reactions. Finally, three examples of a 3-thiophene trifluoroborate reagent but no examples pyridyl reagents have been reported to successfully participate in this reaction.

3 Aims and Objectives

3.1 Hydroxy *iso*-Evoninic Acid

The initial aim of this project was to develop an efficient and novel approach to the total asymmetric synthesis of hydroxy *iso*-evoninic acid (**3**). At the outset several different methods were envisaged that could be employed to do this.

Our overall synthetic strategy was to achieve a directed *ortho* metalation (DoM) at the C4-position of a nicotinic acid derivative, followed by transmetalation of this species to an appropriate transition metal to allow asymmetric 1,4-addition to an α,β -dimethyl substituted enoate. Enolisation of the resulting ester should allow a hydroxy group to be introduced diastereoselectively at the β -carbon by electrophilic oxygenation. Finally, hydrolysis of the ester and nicotinate functionalities should furnish the desired natural product (**Scheme 3.1.1**).



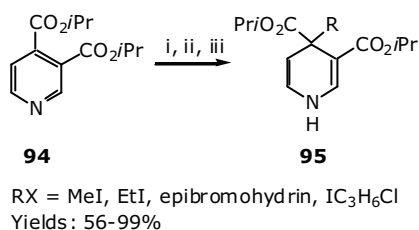
Scheme 3.1.1 – Proposed synthetic strategy for preparation of hydroxy *iso*-evoninic acid.

At the outset our preferred variant of this strategy was to employ rhodium catalysed 1,4-addition methodology. In doing so, we intend to be the first to report the rhodium catalysed 1,4-addition reaction of pyridine derivatives to α,β -unsaturated substrates.

Should this approach prove untenable a number of fallback approaches were envisaged. Our primary fallback strategy was to employ an organocopper based 1,4-addition protocol. There is literature precedent for 1,4-addition of 2- and 3-pyridyl copper reagents but not for 4-pyridyl reagents (see **2.7 1,4-Addition – Pyridyl Copper Complexes**).³⁰ Moreover, asymmetric modifications are known for some of the pyridyl reagents and more generally the use of acyl chiral auxiliaries for the control of cuprate 1,4-addition reactions is well precedented.¹⁰⁷⁻

¹¹¹ Additionally, as discussed above, the use of chiral ferrocenyl diphosphines as ligands in copper-catalysed 1,4-addition of Grignard reagents to cyclic and acyclic enones⁸⁵ and the use of phosphoramidites as chiral ligands in copper-catalysed asymmetric 1,4-addition of diphenylzinc to cyclohexenone have been reported.¹¹²

Alternatively, Donohoe has described the Birch reduction of a 3,4-pyridine diacid **94** to yield a 4-pyridyl carboxylate enolate **95**. This could be quenched with various electrophiles to introduce functionality at the C4-position (**Scheme 3.1.2**).¹¹³

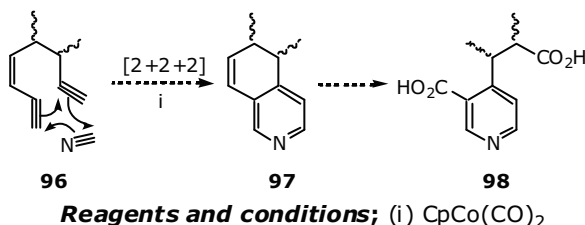


Reagents and conditions; (i) Na, NH₃; (ii) RX; (iii) NH₄Cl

Scheme 3.1.2 – Donohoe’s Birch reduction of 3,4-dicarboxylated pyridine, 2002.

It is possible that this reaction could be adapted to our purposes provided that an α,β -unsaturated ester could be used as the electrophile and 4-decarboxylation with concomitant aromatisation could be achieved.

Finally, we could explore the possibility of generating the pyridine ring by a transition metal mediated [2+2+2] cycloaddition reaction (**Scheme 3.1.3**).¹¹⁴



Scheme 3.1.3 – Possible [2+2+2] cobalt-mediated cycloaddition.

It is envisaged that a substrate containing two terminal alkynes **96** could be reacted with hydrogen cyanide in a [2+2+2] cycloaddition process, mediated by a cobalt catalyst to yield a bicyclic system containing the 3,4-substituted pyridyl ring **97**. Subsequent oxidative cleavage of the alkene bond would then yield the required diacid **98**.

3.2 Absolute and Relative Stereochemistry of Naturally Occurring Hydroxy *iso*-Evoninic Acids

The relative and absolute stereochemistry of hydroxy *iso*-evoninic acid (**3**) in hypoglaunine B (**1**) is not known; we plan to determine this. Since there are two stereogenic centres there are four possible diastereoisomers. Initially we planned to prepare all four isomers (**Fig 3.2.1**).

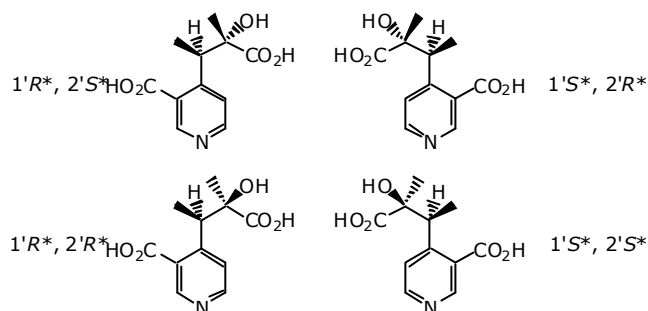


Figure 3.2.1 – Four possible diastereoisomers of hydroxy *iso*-evoninic acid (**3**).

It was proposed to establish the relative stereochemistry of natural hydroxy *iso*-evoninic acid (**3**) by correlation of the ¹H and ¹³C NMR data obtained for the synthetic diastereoisomers with the data published for the natural product, hypoglaunine B (**1**).¹ The determination of the absolute stereochemistry of natural hydroxy *iso*-evoninic acid (**3**) will require correlation of optical rotation with natural material. The absolute stereochemistry of the synthetic material will be determined by anomalous-dispersion X-ray crystallography or by co-crystallisation with a chiral amine of known absolute configuration.

4 Results & Discussion

4.1 Towards Hydroxy-*iso*-Evoninic Acid via Rhodium Catalysed 1,4-Addition

To develop an efficient strategy for the asymmetric synthesis of hydroxy *iso*-evoninic acid (**3**) initial studies focused on a model system, an unsubstituted 4-pyridyl unit. This was to reduce the complexity of the system whilst developing new methodology (**Scheme 4.1.1**).

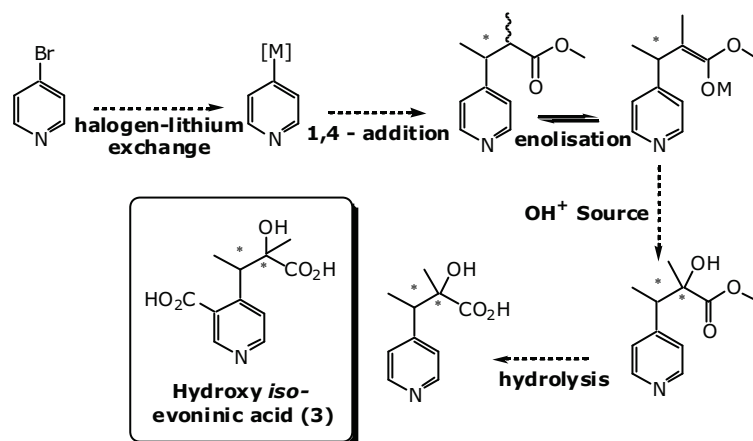


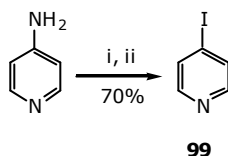
Figure 4.1.1 – Proposed synthetic strategy towards a ‘model’ system.

Once a robust route had been successfully established for the construction of the model system, it was envisaged that modification of the pyridyl unit, by incorporation of a substituent at the C3-position, the first synthesis of hydroxy *iso*-evoninic acid (**3**) could be achieved.

Pyridyl boronic acid derivatives were selected for initial investigation since they represent the most widely documented reagents in the rhodium catalysed 1,4-addition reaction.^{92,98} Phenyl boronic acids have been shown to be resistant to deboronation under the reaction conditions and moreover, previous work in this area has exemplified the addition of both electron deficient and *ortho*-substituted phenyl boronic acids to a variety of Michael acceptors.^{89,90}

4.1.1 Synthesis of 4-Pyridyl Boronic Acid Ester Derivatives

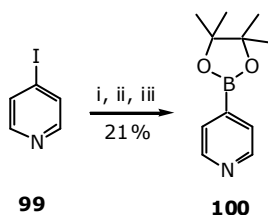
The preparation of 4-pyridyl boronic acid derivatives was achieved using 4-iodopyridine as the starting material, since 4-bromopyridine proved rather capricious. 4-Iodopyridine **99** was prepared by diazotisation of 4-aminopyridine followed by treatment with potassium iodide, to furnish iodide **99** in good yield (70%) (**Scheme 4.1.1.1**).¹¹⁵



Reagents and conditions; (i) NaNO₂; (ii) HBF₄, -20 °C, sat. KI

Scheme 4.1.1.1 – Preparation of 4-iodopyridine **99**.

Treatment of iodide **99** with *n*-BuLi in Et₂O followed by sequential addition of tributylborate, pinacol and acetic acid obtaining pinacol ester **100**¹¹⁵ albeit in low yield (21%) (**Scheme 4.1.1.2**).



Reagents and conditions; (i) *n*-BuLi, Et₂O, -60 °C; (ii) B(OBu)₃; (iii) pinacol AcOH

Scheme 4.1.1.2 – Preparation of 4-pyridyl boronic acid pinacol ester **100**.

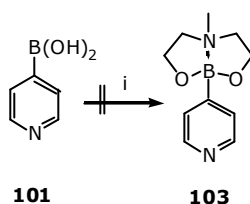
Experiments probing the utility of this substrate, alongside the commercially available pyridyl boronic acid **101** in the rhodium catalysed 1,4-addition reaction were instigated.

As a prelude to this, a literature reaction was repeated to ensure that the chemistry was reproducible in our hands. The rhodium catalysed 1,4-addition reaction between phenyl boronic acid and methyl crotonate was successfully repeated to give the desired phenyl addition product **102** in 78% yield (**Table 4.1.1.1, entry 1, pp 57**).⁹¹

Confident the reaction conditions were reproducible, the rhodium catalysed 1,4-addition reaction of pyridyl boronic acid **101** and pinacol ester **100** to methyl crotonate was attempted (**Table 4.1.1.1, entries 2 & 3, pp 57**). To our disappointment, both cases resulted in the deboronation of the starting material

as revealed by ^1H NMR analysis: no aromatic signals were found. This may be explained by the fact that pyridyl borate species are readily deboronated, in the presence of H_2O , which is a pre-requisite for the reaction (i.e. deboronation gives pyridine, which is volatile).⁹⁰

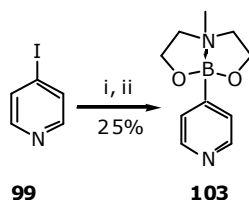
To circumvent this problem the more stable 4-pyridyl *N*-methyldiethanolamine borate **103**¹¹⁶ species was examined. Initial attempts to prepare this substrate using standard protocols i.e. treatment of pyridyl boronic acid **101** with *N*-methyldiethanolamine in the presence of magnesium sulfate, did not afford the anticipated borate **103** (**Scheme 4.1.1.3**).¹¹⁶



Reagents and conditions; (i) *N*-Methyl diethanolamine, MgSO_4 , CH_2Cl_2 , rt, 18 h

Scheme 4.1.1.3 – Attempted synthesis of 4-pyridyl *N*-methyldiethanolamine borate **103**.

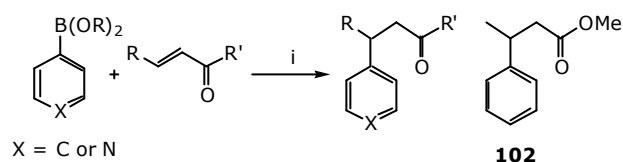
A procedure employing a modification of the method used to prepare the pinacol ester **100**, furnished the desired borate **103** in only 25% yield (**Scheme 4.1.1.4**).



Reagents and conditions; (i) *n*-BuLi, Et_2O , -60°C (ii) $\text{B}(\text{OBu})_3$, *N*-Methyl diethanolamine

Scheme 4.1.1.4 – Preparation of 4-pyridyl *N*-methyldiethanolamine borate **103**.

Attempted 1,4-addition of this substrate to methyl crotonate was unsuccessful. Deboronation of the starting material was again evident by the absence of aromatic signals in the ^1H NMR (**Table 4.1.1.1, entry 4, pp 57**).



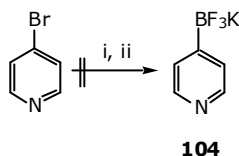
Reagents and conditions; (i) Rh(acac)(C₂H₄)₂, (S)-BINAP, dioxane/H₂O, 102°C

Entry	Substrate	ArB(OR) ₂	Outcome
1			102 in 78% yield
2			no product/ deboronation of ArB(OR) ₂
3			no product/ deboronation of ArB(OR) ₂
4			no product/ deboronation of ArB(OR) ₂

Table 4.1.1.1 – Summary of results for the 1,4-addition reactions of 4-pyridyl boronates to methyl crotonate.

Owing to the lack of success in using 4-pyridyl boronic acid derivatives in the 1,4-addition reaction to methyl crotonate, the preparation of a potassium trifluoroborate salt, as a potentially more stable analogue of 4-pyridyl boronic acid, was considered. These hypervalent derivatives are reported to be very reactive and highly resistant to deboronation and furthermore, have been shown to be competent substrates in rhodium catalysed 1,4-addition reactions.

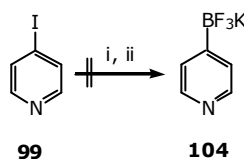
Preparation of the 4-pyridyl potassium trifluoroborate salt using modified conditions for the preparation of the analogous phenyl derivatives gave disappointing results.¹¹⁷ The reaction gave a number of unidentifiable pyridyl containing products as observed by ¹H NMR analysis none of which could be assigned to that of the desired product **104** (Scheme 4.1.1.5).



Reagents and conditions; (i) *n*-BuLi, THF, -78°C; (ii) B(OBu)₃, aq. HKF₂

Scheme 4.1.1.5 –Attempted synthesis of 4-pyridyl potassium trifluoroborate salt **104** using a modification of Genet’s method.

A modified method using 4-iodopyridine **99** as the starting material was attempted, but once again resulted in the formation of a number of unassignable products (**Scheme 4.1.1.6**).



Reagents and conditions; (i) *n*-BuLi, THF, -78°C; (ii) B(OBu)¹₃, aq. HKF₂

Scheme 4.1.1.6 – Attempted synthesis of 4-pyridyl trifluoroborate potassium salt **104** from 4-iodopyridine **99**.

Difficulties in preparing this substrate using standard protocols and the lack of literature precedent for the synthesis of this particular pyridyl salt dissuaded further exploration into the preparation of this substrate.

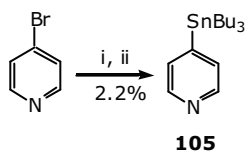
In light of these results it was clear that 4-pyridylboronic acid derivatives, even particularly stable ones, such as the diethanolamine derivative, were unsuitable substrates for this reaction, principally because they deboronated too readily under the aqueous reaction conditions. As a result, investigations into 4-pyridyl metal species that were anticipated to be more stable under the reaction conditions were initiated.

4.1.2 Synthesis of 4-Pyridyl Trialkylstannane Reagents

Trialkylstannane derivatives are attractive alternatives to boronic acids in rhodium catalysed 1,4-addition reactions for two reasons. First, trialkylstannane derivatives are less susceptible to destannylation than boronic acids are to deboronation under aqueous conditions and thus are expected to be more stable under the given reaction conditions. Secondly, the proposed catalytic cycle by Oi (see **2.4.1 Reaction Mechanism**)¹¹⁸ implies that the role of H₂O in stannane 1,4-addition reactions is secondary to that of the catalytic cycle, and so it is

envisaged that H₂O may potentially be withheld from the reaction with the view to isolate the tin enolate product in the first instance. This would not only circumvent any potential problems with regards to destannylation, but moreover, would provide a platform for the exploration of α -hydroxylation reactions using the tin enolate with HO⁺ sources to furnish the α -hydroxy product (which is required for the natural product target) without the need for a separate enolisation step.

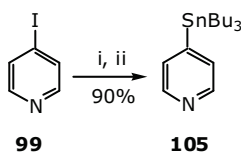
Unexpectedly, the preparation of 4-pyridyl tributylstannane **105**¹¹⁹ using literature conditions proved challenging. Treatment of 4-bromopyridine with phenyl lithium in Et₂O, followed by tributyl stannanyl chloride gave stannane **105** in a very low yield of 2.2%.¹¹⁹ This extremely low yield partly reflected the problems experienced with purification of this compound. One major problem was an aromatic impurity (from the lithiating reagent) (**Scheme 4.1.2.1**).



Reagents and conditions; (i) *n*-PhLi, Et₂O, -78 °C; (ii) SnBu₃Cl

Scheme 4.1.2.1 – Preparation of 4-pyridyl tributylstannane **105** using PhLi/ 4-pyridyl bromide.

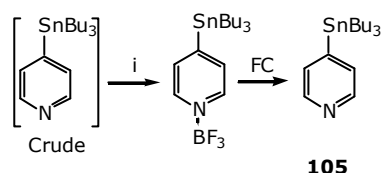
A more efficient formation of the required product was realised by reverting back to the more reliable 4-iodopyridine **99**, which gave stannane **105** in a crude yield of 90% (**Scheme 4.1.2.2**).



Reagents and conditions; (i) *n*-BuLi, Et₂O, -60 °C; (ii) SnBu₃Cl

Scheme 4.1.2.2 – Preparation of 4-pyridyl tributylstannane **105** using *n*-BuLi/ 4-pyridyl iodide **99**.

Complications were again met with the purification of this compound, this time due to the presence of an aliphatic containing by-product (i.e. containing butyl groups from the *n*-BuLi). It is well documented that one drawback in employing tin reagents in synthesis, is the difficult separation of the desired product from the tin residues. Flash chromatography is difficult due to the streaking of tin compounds on silica. Various attempts to purify the 4-pyridyl trialkylstannane including the preparation of the trifluoroborate adduct led to no significant improvement in purity as evidenced by CI-MS analysis, which showed the presence of a molecular ion at 739 *m/z* (**Scheme 4.1.2.3**).¹²⁰⁻¹²⁵



FC - Flash Chromatography

Reagents and conditions; (i) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, Et_2O , 0°C - rt

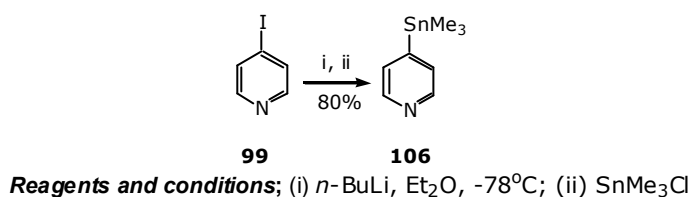
Scheme 4.1.2.3 – Purification by 4-pyridyl tributylstannane by the formation of a trifluoroborate adduct.

Finally, reverse phase C18 chromatography allowed for removal of the unknown impurity (m/z 739) to give tributyl stannane **105** in 87% yield.

With the tributyl stannane **105** in hand, the rhodium catalysed 1,4-addition reaction of this substrate to methyl crotonate was attempted. The first attempt was made using the *standard conditions* for phenyl boronic acids (**Table 4.1.2.1, entry 1, pp 62**). These conditions did not result in any reaction taking place.⁹⁰ Encouragingly, the starting material was recovered quantitatively, supporting the hypothesis that organostannane derivatives are more stable than the corresponding boronates to the rhodium catalysed 1,4-addition reaction conditions. The second attempt was made using those conditions described for the use of phenyl trialkyl stannanes in the reaction. Once again, no reaction was observed, with almost quantitative recovery of the starting material (**Table 4.1.2.1, entry 2, pp 62**).

Tributyl stannane derivatives are known to be significantly less reactive than their trimethyl stannane analogues.⁹⁷ As a prelude to the preparation of the more toxic 4-pyridyl trimethyl stannane **106**, two rhodium catalysed 1,4-addition literature reactions with the corresponding phenyl tributyl- and phenyl trimethylstannanes were repeated to establish the exact magnitude of the difference in reactivity. The 1,4-addition of these stannanes to 4-phenylbut-3-ene-2-one provided us with some interesting results.⁹⁷ The phenyl tributyl stannane was reported to yield the desired product in <2 h in 70% yield. However, none of the desired 1,4-addition product (compound **107**) was detected after 2 h and only trace amounts of the desired 1,4-adduct was detected after 24 h (**Table 4.1.2.1, entry 3, pp 62**). The phenyl trimethyl stannane was reported to yield the desired 1,4-addition product (compound **107**) after 2 h in 92% yield; in our hands, a 78% yield was obtained after 2 h (**Table 4.1.2.1, entry 4, pp 62**). These results underscored the higher reactivity of trimethyl stannanes relative to the analogous tributyl stannane.⁹⁷

Consequently, the preparation of the 4-pyridyl trimethyl stannane **106** was undertaken using the same protocol as described for the tributyl analogue (**Scheme 4.1.2.4**).¹²⁶



Scheme 4.1.2.4 – Preparation of 4-pyridyl trimethyl stannane **106**.

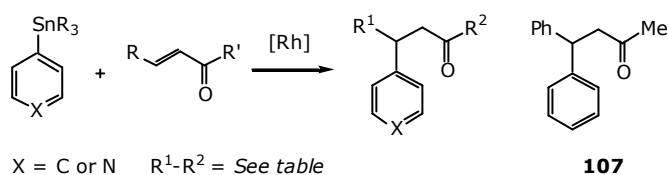
Problems with the purification of this substrate were also encountered. The most persistent problem was the presence of unreacted starting material, iodide **99**. Several attempts were made to resolve this problem: initially reverse-phase C18 chromatography¹²² was employed which had been previously successful in the purification of the tributyl analogue. Unfortunately, the desired product **106** co-ran with the starting iodide **99**. Fortuitously, purification was achieved by conventional flash chromatography in good yield (80%).

With this substrate in hand, the rhodium catalysed 1,4-addition to 4-phenyl but-3-ene-2-one was attempted. To our disappointment, none of the desired 1,4-addition product was detected, with only quantitative recovery of starting material (**Table 4.1.2.1, entry 5, pp 62**). We subsequently resolved to perform the reaction at an elevated temperature (1,4-dioxane at 100 °C) (**Table 4.1.2.1, entry 6, pp 62**) and also with the addition of LiF (in the hope of promoting stannane nucleophilicity), however both reactions met with failure, with stannane **106** isolated on both occasions (**Table 4.1.2.1, entry 7, pp 62**).¹²⁷

The upshot of all the aforementioned studies was that both the 4-pyridyl tributyl **105** and trimethyl **106** stannanes were too unreactive towards the rhodium-catalysed 1,4-addition reaction conditions and modifications thereof. These reagents however were more stable than the foregoing boronic acid derivatives, clearly indicating that a 4-pyridyl metal substrate that displayed comparable stability to the stannanes but higher reactivity was required.

It became clear at this point that more would have to be done to activate the pyridyl substrates towards the reaction. It was also apparent that the nucleophilicity of the C4 position on the pyridine ring, (required for transmetallation onto the rhodium catalyst), is heavily compromised by the electronegativity of the *para* nitrogen atom in the ring. We reasoned that the

presence of an electron-donating group on the pyridine ring would increase the nucleophilicity of the C4 position and counteract the electron-withdrawing effects of the pyridine nitrogen.



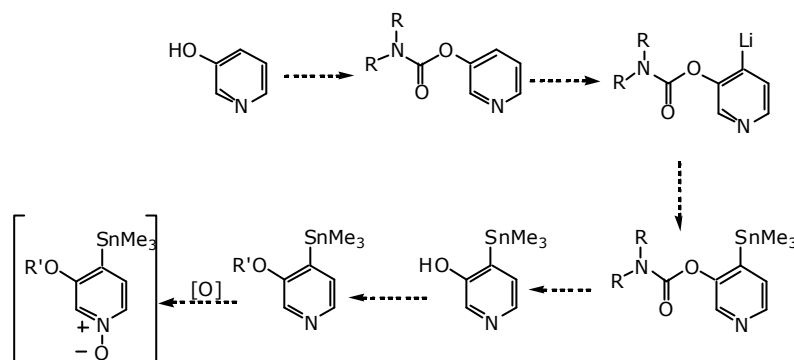
Entry	Substrate	ArSnR ₃	Conditions	Outcome
1			Rh(acac)(C ₂ H ₄) ₂ (S)-BINAP dioxane/H ₂ O, 102°C	no reaction
2			[Rh(cod)(MeCN) ₂]BF ₄ 3 mol% THF/H ₂ O, 60°C	no reaction
3			[Rh(cod)(MeCN) ₂]BF ₄ 3 mol% THF/H ₂ O, 60°C	trace product after 24 h
4			[Rh(cod)(MeCN) ₂]BF ₄ 3 mol% THF/H ₂ O, 60°C	78% yield after 2 h, compound 107
5			[Rh(cod)(MeCN) ₂]BF ₄ 3 mol% THF/H ₂ O, 60°C	no reaction
6			[Rh(cod)(MeCN) ₂]BF ₄ 3 mol% dioxane/H ₂ O, 102°C	no reaction
7			[Rh(cod)(MeCN) ₂]BF ₄ 3 mol%, LiF dioxane/H ₂ O, 102°C	no reaction

Table 4.1.2.1 – Summary of results for 1,4-addition reactions of 4-pyridyl stannanes to methyl crotonate and/or 4-phenyl but-3-ene-2-one.

4.1.3 Synthesis of 3-Substituted-4-Pyridyl Trialkylstannane Reagents

The preparation of 4-pyridyl trimethyl stannanes, containing an electron-donating substituent (e.g. OR) at the C3-position of the pyridine ring was considered. It was anticipated that the advantages of an electron donating substituent at the C3 position would be two-fold: First, it would help to counteract the electron-

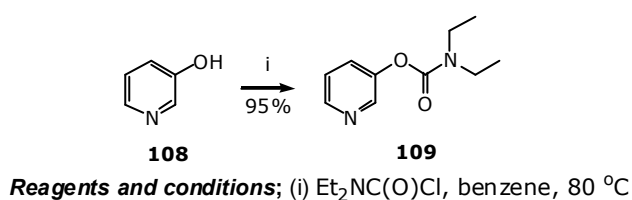
withdrawing effects of the pyridyl nitrogen (as mentioned previously), hence making the molecule more nucleophilic at the C4-position. Secondly, the substituent could constitute a functional handle for elaboration to a carboxylic acid as required in the natural product target [e.g. via Pd(0) catalysed carbonylation of a derived triflate] (**Scheme 4.1.3.1**).



Scheme 4.1.3.1 – Strategy to synthesise a more reactive 4-pyridyl trimethylstannane reagent.

As outlined in the above scheme, an electron-rich stannane in combination with an *N*-oxide derivative may further enhance the reactivity of the system by alleviating some of the electron withdrawing influence of the pyridyl nitrogen by effectively “pushing” electron density onto the nitrogen.¹²⁵

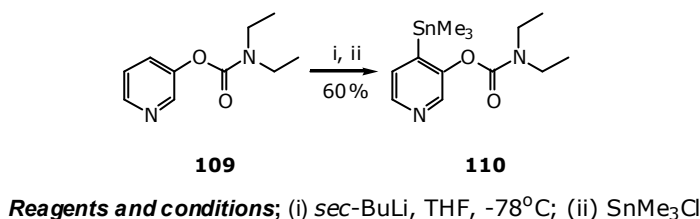
A survey of the literature showed that carbamate groups were excellent *ortho* directing groups and so experiments into the preparation of more reactive stannanes were initiated by the preparation of 3-pyridyl carbamate **109**.¹²⁸ The product was furnished by reaction of hydroxy pyridine **108** with carbamyl chloride in excellent yield (99%) (**Scheme 4.1.3.2**).¹²⁸



Scheme 4.1.3.2 – Preparation of 3-pyridyl carbamate **109**.

The DoM of this substrate at the C4-position regioselectivity over the C2-position of the pyridine ring proved to be challenging since the original report failed to provide an experimental procedure.^{129,130} Initial attempts using, 1.1 equivalents of *sec*-BuLi and TMEDA at –78 °C, followed by the addition of trimethyl stannyl chloride were unsuccessful. Several experiments were performed with a variety of solvents and reagents to qualitatively establish optimum conditions for the reaction, where discrimination between the C2 and C4 positions on the pyridine

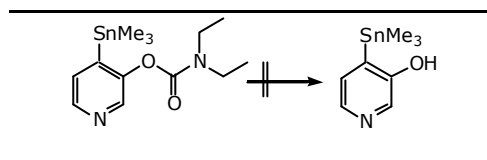
ring was sought. This finally resulted in the use of 2.2 equivalents of *sec*-BuLi and TMEDA to afford the desired stannane in excellent regiocontrol (100% C4-substituted product). Attempts to purify the compound by reduced pressure distillation resulted in the decomposition of the compound to a more complex mixture by ^1H NMR. Fortuitously, given our problems with stannane compounds, purification by flash chromatography furnished stannane **110** in 60% yield (**Scheme 4.1.3.3**).^{129,130}



Scheme 4.1.3.3 – Preparation of 4-trimethylstannyl-3-diethylcarbamyl pyridine **110**.

Perhaps unsurprisingly, the rhodium catalysed 1,4-addition of this substrate to both 4-phenyl but-3-ene-2-one and methyl crotonate was unsuccessful (**Table 4.1.3.3, entries 1 & 2, pp 69**). It seems likely that the electronics of the system are not significantly improved relative to the parent compound (i.e. the unsubstituted stannane **106**), hence a method to remove the carbamate functionality to afford the free alcohol (i.e. to give a more electron rich substrate) was sought.

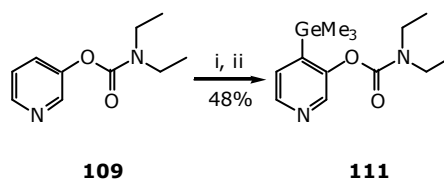
Initial attempts to remove the carbamate group by hydrolysis using sodium methoxide, or sodium hydroxide in H₂O were unsuccessful (**Table 4.1.3.1, entries 1 & 2**).¹³¹ In both cases the stannyl functionality was found to be base-sensitive: the required hydrolysis and the unwanted destannylation of the substrate occurred in one pot to give 3-hydroxy pyridine. Next, reductive removal of the carbamate group with LiAlH₄ was attempted. However, this resulted in the degradation of the starting material to form a number of unidentifiable products by ^1H NMR analysis (**Table 4.1.3.1, entry 3**).¹³² Similarly, DIBAL and Superhydride[®] reductions gave disappointing results (**Table 4.1.3.1, entries 4 & 5**). It was clear that the removal of carbamate functionality whilst preserving the stannane was not going to be possible.



Entry	Conditions	Outcome
1	NaOMe/MeOH	no evidence of product
2	NaOH/MeOH	no evidence of product/ destannylation observed
3	LiAlH ₄	no evidence of product
4	LiB(C ₂ H ₅) ₃ H	no evidence of product/ starting material recovered
5	DIBAL	no evidence of product

Table 4.1.3.1 - Attempted removal of the carbamate group.

For comparative studies, the preparation of the corresponding germanium analogue **111** was undertaken. This substrate was expected to be more stable to basic conditions than the analogous stannane (**Scheme 4.1.3.4**).¹³³



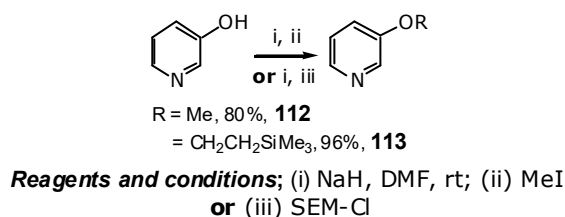
Reagents and conditions: (i) *sec*-BuLi, THF, -78°C; (ii) GeMe₃Br

Scheme 4.1.3.4 – Preparation of 4-trimethylgermyl-3-diethylcarbamyl pyridine **111**.

Attempts to remove the carbamate group by hydrolysis using sodium hydroxide in MeOH were unsuccessful, although as expected no degermylation of the starting material was detected.

Owing to the unsuccessful removal of the carbamate group from stannane **110**, we resolved to find an alternative directing group for the lithiation step in accord with our strategy. Both the methyl ether **112** and the SEM ether **113** have been documented to successfully undergo DoM at the C4-position selectively over the C2-position of the pyridine ring under appropriate conditions.¹³²

Both substrates were prepared by deprotonation of 3-hydroxy pyridine with NaH, followed by the addition of the electrophile (MeI and SEM-Cl to give products **112** and **113**, respectively) (**Scheme 4.1.3.5**).^{132,134}

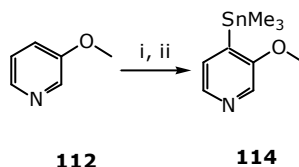


Scheme 4.1.3.5 – Preparation of methoxy pyridine **112** and SEM protected 3-hydroxy pyridine **113**.

DoM of methyl ether **112** using literature conditions (i.e. MeLi) proved difficult since the original report failed to provide an experimental procedure. The results of these studies are outlined below (**Table 4.1.3.2**).¹³⁵

First, we evaluated the use of MeLi in Et₂O and in THF at –78 °C; disappointingly neither set of conditions resulted in the formation of the desired product (**Table 4.1.3.2, entries 1 & 2**). The addition of TMEDA to the reactions did not resolve the problem (**Table 4.1.3.2, entries 3 & 4**).¹³⁶ The TMEDA is known to prevent the aggregation of the lithium base by co-ordinating to the lithium, making a more efficient species for selective deprotonation.

Following this, the lithiation conditions successful for the preparation of the 3-pyridyl-4-trimethylcarbamyl stannane **110** were investigated, but these also failed to give the desired product. Finally, given that starting material was recovered in all the reactions described above, the influence of temperature was examined next. The reaction at –40 °C was once again unsuccessful, with only the quantitative recovery of starting material (**Table 4.1.3.2, entry 6**). Subsequent increases in temperature by 10 °C increments revealed that the reaction at 20 °C gave the most promising results. The reaction in THF was unsuccessful. It appeared that the MeLi reacted with the solvent causing it to polymerise and the reaction mixture to turn black (**Table 4.1.3.2, entry 7**). The reaction in benzene did not discriminate between deprotonation at the C2 and C4 positions of the pyridine ring, giving a mixture of both the C2- and C4-substituted products in equal amounts (**Table 4.1.3.2, entries 8 & 9**). However, the reaction in Et₂O was completely regioselective, exclusively affording the desired C4 stannane **114** (75%).¹³⁷

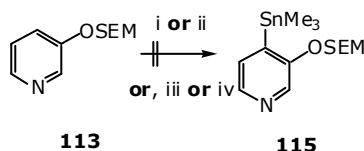


Reagents and conditions; (i) MeLi; (ii) SnMe₃Cl

Entry	Lithating Agent	Solvent	Temp/°C	Additive	Outcome
1	MeLi	Et ₂ O	-78 °C	-----	no evidence of product
2	MeLi	THF	-78 °C	-----	no evidence of product
3	MeLi	THF	-78 °C	TMEDA	no evidence of product
4	MeLi	Et ₂ O	-78 °C	TMEDA	no evidence of product
5	sec-BuLi	THF	-78 °C	TMEDA	no evidence of product
6	MeLi	THF	-40 °C	TMEDA	no evidence of product
7	MeLi	THF	rt	-----	no evidence of product
8	MeLi	Et ₂ O	rt	-----	successful - see text
9	MeLi	benzene	rt	-----	successful - see text

Table 4.1.3.2 - DoM/stannylation of 3-methoxy pyridine **112**.

Several conditions, including those reported in the literature i.e. using *tert*-BuLi were also attempted to achieve this transformation. Unfortunately, no evidence of the directed *ortho*-metalated product, stannane **115** was ever observed (**Scheme 4.1.3.6**).^{132,138}



Reagents and conditions; (i) *tert*-BuLi, THF, -78°C, SnMe₃Cl; **or** (ii) *sec*-BuLi, THF, -78°C, SnMe₃Cl **or** (iii) MeLi, Et₂O, SnMe₃Cl **or** (iv) *tert*-BuLi, -78 -0 °C, THF or Et₂O, SnMe₃Cl

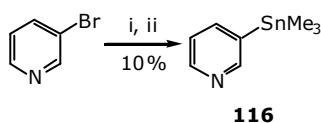
Scheme 4.1.3.6 - Attempted DoM/stannylation of 3-SEM protected hydroxy pyridine **113**.

With an electron rich substrate in hand (i.e. 3-methoxy-4-trimethyl stannane **114**) we decided to test this substrate in the rhodium catalysed 1,4-addition reaction with both phenyl but-3-ene-2-one and methyl crotonate (**Table 4.1.3.3, entries 3 & 4, pp 69**).

Analysis of the reactions after 2 h showed no observable reaction and no visible degradation of the starting materials. Analysis thereafter showed no significant changes. Addition of one equivalent of LiF to the reaction also resulted in no improvement.¹³⁹ Subsequent examination of the crude reaction mixture by ¹H NMR analysis revealed additional tin containing signals. This was consistent with the degradation of the stannane starting material. These results were disappointing, since it had been anticipated that this electron-rich substrate would be more reactive due to the increased nucleophilicity of the C4-position. Given these results, the preparation of further electron-rich substrates was abandoned.

It was decided that an investigation into the reactivity of 3-pyridyl trimethyl stannane would allow us to assess the difference in reactivity between the C4 and C3 positions of the pyridine ring. The C3-position on the pyridine ring is significantly less deactivated by the pyridine nitrogen and so should display similar reactivity to phenyl trimethylstannane substrates; which readily undergo this reaction.

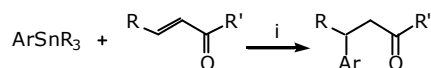
Preparation of the 3-pyridyl trimethyl stannane **116**¹⁴⁰ was accomplished by treatment of 3-bromopyridine with *n*-BuLi at -78 °C, albeit in only 10% yield (**Scheme 4.1.3.8**).



Reagents and conditions; (i) *n*-BuLi, Et₂O, -78°C; (ii) SnMe₃Cl

Scheme 4.1.3.7 – Synthesis of 3-pyridyl trimethyl stannane **116**.

The rhodium catalysed 1,4-addition of both the 4-pyridyl and 3-pyridyl stannanes to 4-phenyl but-3-ene-2-one were attempted in parallel. No reaction was observed with either substrate after 24 h (**Table 4.1.3.3, entries 5 & 6, pp 69**).



Reagents and conditions: (i) $[\text{Rh}(\text{cod})(\text{MeCN})_2]\text{BF}_4$, THF, H_2O , 60 °C

Entry	Substrate	ArSnR ₃	Outcome
1			no reaction
2			no reaction
3			no reaction
4			no reaction
5			no reaction
6			no reaction

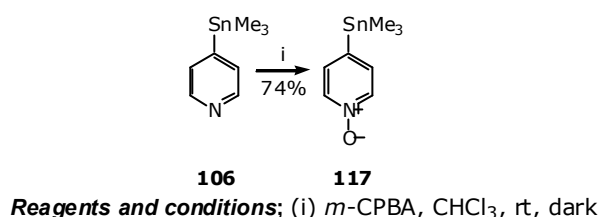
Table 4.1.3.3 – Attempted 1,4-addition reactions of arylstannanes to methyl crotonate and/or phenyl but-3-ene-2-one.

The results from these studies suggested that the lack of reactivity of the foregoing stannane substrates towards rhodium catalysed 1,4-addition was not entirely that the substrates were too electron-deficient to undergo the reaction, but that the lone pair on the pyridine nitrogen was interfering with the reaction pathway presumably as a Lewis base. To confirm this hypothesis a strategy to 'block' the pyridine nitrogen was instigated.

4.1.4 Protecting the Pyridine Nitrogen: Synthesis of *N*-Oxide, *N*-Methyl salts and *N*-TBS Pyridinium Salts

The inspiration for this strategy was based on a similar strategy employed by Zoltewicz who prepared the *N*-oxide and various methylated pyridinium salts of 4-pyridyl tributyl stannane in his endeavours to conduct palladium-catalysed cross coupling reactions with pyridyl derivatives.^{141,142}

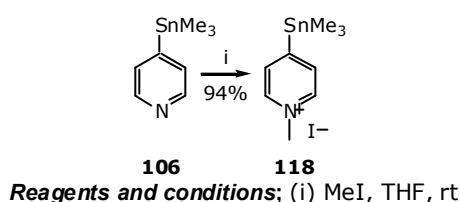
Preliminary investigations began by reverting back to the *mono*-substituted pyridyl stannane **106** and preparing its *N*-oxide **117** by reaction with *m*CPBA. The *N*-oxide **117** was obtained in good yield (74%) (**Scheme 4.1.4.1**).¹²⁶



Scheme 4.1.4.1 – Synthesis of 4-pyridyl trimethyl stannane-*N*-oxide **117**.

The rhodium catalysed 1,4-addition of *N*-oxide **117** to methyl crotonate resulted in quantitative recovered of starting material (**Table 4.1.4.1, entry 1, pp 71**). This was perhaps expected since *N*-oxides are significantly nucleophilic at oxygen.

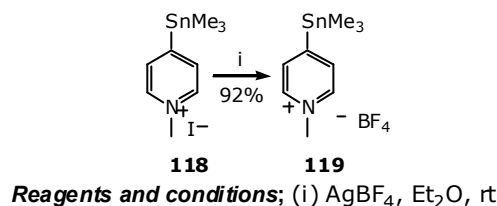
The preparation of pyridinium salts were investigated next. The methyl iodide pyridinium salt **118**¹⁴³ was successfully prepared by reaction of the stannane **106** with MeI in excellent yield (94%) (**Scheme 4.1.4.2**).^{141,143}



Scheme 4.1.4.2–Synthesis of 4-pyridyl trimethylstannane methyl iodide pyridinium salt **118**.

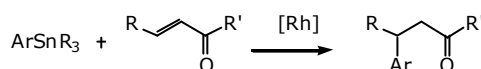
Anxious to see if this substrate was the solution to our problem, the rhodium catalysed 1,4-addition reaction to methyl crotonate was tried (**Table 4.1.4.1, entry 2, pp 71**). There appeared to be no evidence of the product, possibly due to trace amounts of pyridine poisoning the rhodium catalyst. Unfortunately, there also appeared to be visible degradation of the starting material by crude ¹H NMR analysis. It was thought that the iodide counterion could potentially facilitate destannylation of the substrate (halides having a high affinity for tin metal centres).

Subsequently, we resolved to change the counterion from iodide to the tetrafluoroborate, to match the counterion of the rhodium catalyst. This was accomplished by reacting the methyl iodide pyridinium salt **118** with silver tetrafluoroborate (**Scheme 4.1.4.3**).



Scheme 4.1.4.3 – Synthesis of methyl tetrafluoroborate pyridinium salt **119** from the corresponding methyl iodide pyridinium salt **118**.

Isolation of the desired tetrafluoroborate pyridinium salt **119** was possible in 92% yield.¹⁴² The rhodium catalysed 1,4-addition of this pyridinium salt to methyl crotonate were subsequently attempted (**Table 4.1.4.1, entries 3, pp 71**). Unfortunately, none of the anticipated 1,4-addition product was obtained; once again destannylation of the starting material was evident, fuelling the hypothesis that the halide counterion was a problem in this reaction, (fluoride ions also have a high affinity for tin centres).



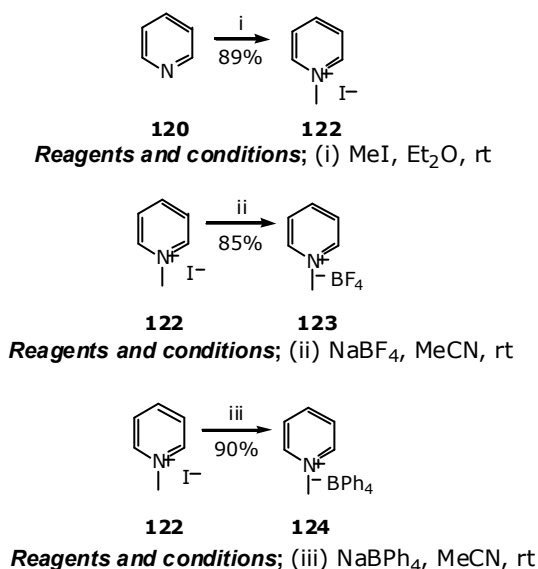
Entry	Substrate	ArSnR ₃	Conditions	Outcome
1			[Rh(cod)(MeCN) ₂]BF ₄ 3 mol% THF/H ₂ O, 60°C	no reaction
2			[Rh(cod)(MeCN) ₂]BF ₄ 3 mol% THF/H ₂ O, 60°C	no product/ degradation of SM
3			[Rh(cod)(MeCN) ₂]BF ₄ 3 mol% THF/H ₂ O, 60°C	no product/ degradation of SM

Table 4.1.4.1 - Summary of results for 1,4-addition reactions of arylstannane *N*-methyl pyridinium salts to methyl crotonate.

To definitively determine whether the pyridine nitrogen was impeding the 1,4-addition reaction, either by acting as a nucleophile/ligand on the rhodium or the tin centres, it was decided to 'spike' the literature reaction between phenyl trimethyl stannane and methyl crotonate⁹⁷ with various pyridine derivatives and monitor their effects on the progress of the reaction.

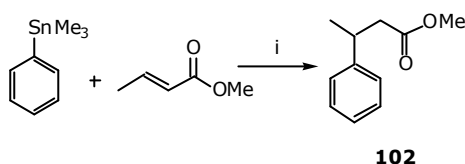
The unspiked reaction proceeded in 78% after 2 h in our hands (**Table 4.1.4.2, entry 1, pp 73**).⁹⁷ The reaction doped with pyridine **120** (**Table 4.1.4.2, entry 2, pp 73**) did not proceed to give the 1,4-addition product, reinforcing the idea that a nucleophilic pyridine nitrogen is not tolerated in the reaction. Moreover, the reaction spiked with the *N*-oxide of picoline **121** (**Table 4.1.4.2, entry 3, pp 73**) was also unsuccessful: a heavy precipitate of a black solid was also observed after 24 h, presumably due to the degradation of the organostannane species and/or the rhodium catalyst. This supported the original findings that *N*-oxide **117** was not the answer to the problem.

N-Methyl pyridinium salts with varying counterions were evaluated as additives next. The iodide **122**, was prepared by treating pyridine with methyl iodide. Reaction of this salt with sodium tetrafluoro- or tetraphenyl- borates then gave pyridinium salts **123** and **124**, respectively (**Scheme 4.1.4.4**).¹⁴¹



Scheme 4.1.4.4 – Synthesis of methyl iodide **122**, tetrafluoroborate **123** and tetraphenylborate **124** pyridinium salts.

The subsequent spiking reactions gave interesting results (**Table 4.1.4.2**).



Reagents and conditions; (i) $[\text{Rh}(\text{COD})(\text{MeCN})_2]\text{BF}_4$, Additive, THF, H_2O , reflux

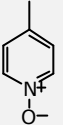
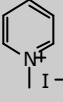
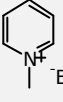
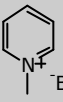
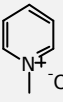
Entry	Additive	Outcome
1	-----	78%
2	 120	no reaction
3	 121	no reaction
4	 122	no product/ degradation of SM
5	 123	no product/ degradation of SM
6	 124	70%
7	 126	85%

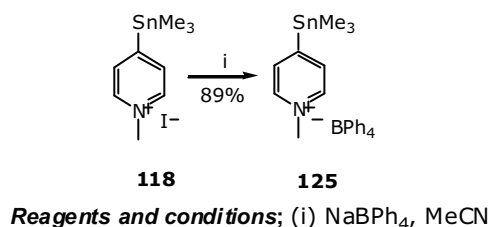
Table 4.1.4.2 – Summary of results for the “spiking” of the 1,4-addition of phenyl trimethyl stannane to methyl crotonate with various pyridine derivatives.

The reactions spiked with both the methyl iodide **122** and tetrafluoroborate **123** pyridinium salts resulted in the degradation of the starting material (**Table 4.1.4.2, entries 4 & 5, pp 73**). However, we were delighted to find that the reaction spiked with the methyl tetraphenylborate pyridinium salt **124** resulted in the formation of the desired product **102** albeit in a lower yield than for the unspiked reaction (70% *cf.* 82% after 2 h)⁹⁷ (**Table 4.1.4.2, entry 6, pp 73**).

It appeared that halide based counterions were incompatible with this reaction, probably due to the high affinity of halide anions for tin centres. This theory was

supported by analysis of the crude reaction mixtures by ^1H NMR; which revealed that the stannane reagent had disappeared with no consumption of the α,β -unsaturated substrate (**Table 4.1.4.2, entries 4 & 5, pp 73**).

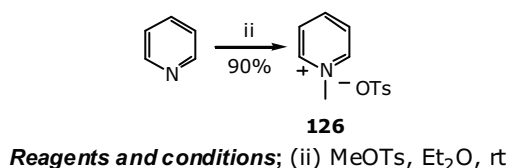
Next, the 4-pyridyl stannane tetraphenylborate pyridinium salt **125** was prepared from the corresponding methyl iodide pyridinium salt **118** on treatment with sodium tetraphenylborate in 89% yield (**Scheme 4.1.4.5**).¹⁴¹



Scheme 4.1.4.5 - Synthesis of 4-trimethylpyridinium methyl tetraphenylborate salt **125**.

Rather unexpectedly, the rhodium catalysed 1,4-addition reaction of this pyridinium salt **125** to methyl crotonate resulted in the isolation of the *phenyl* addition product **102** in moderate yield (68%). Clearly the phenyl group came from the tetraphenyl borate counterion (**Table 4.1.4.3, entry 1, pp 76**). The phenyl group that transferred in the original spiking reaction could have been provided by either the substrate or the counterion – giving a false positive result. Tetraphenyl borates are known to act as a source of nucleophilic phenyl.¹⁴⁴

On re-examination of Zoltewicz's work an interesting observation was noted. He reported that the use of a tosylate counterion was preferable in his Stille-type cross-coupling reactions because of its inert nature, owing to its large size and non-nucleophilicity.¹⁴¹ Consequently, the methyl tosylate pyridinium salt **126** was prepared in 90% yield (**Scheme 4.1.4.6**).¹⁴⁵

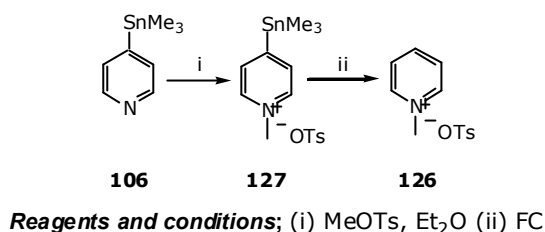


Scheme 4.1.4.6 - Preparation of methyl tosylate pyridinium salt **126** from pyridine.

Subsequent employment of this salt as an additive in the rhodium catalysed 1,4-addition reaction of phenyl trimethyl stannane to methyl crotonate gave a promising result. The expected phenyl addition product **102** was isolated in 85% yield (**Table 4.1.4.2, entry 7, pp 73**). This was the first pyridinium salt to remain inert during the course of the spiking reaction and to unambiguously give

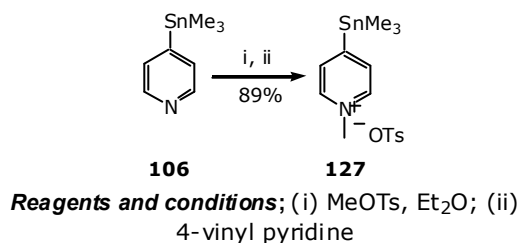
the desired *phenyl* addition product as the result of addition by the phenyl trimethyl stannane.

Encouraged by the success of this spiking reaction the preparation of corresponding 4-pyridyl stanane pyridinium salt was instigated. Stannane **106** was treated with methyl tosylate in Et₂O overnight. Crude ¹H NMR analysis showed the formation of the desired pyridinium salt **127**; unfortunately, purification by reverse phase C18 chromatography resulted in destannylation of the product (pyridinium salt **126**) (**Scheme 4.1.4.7**).¹⁴¹



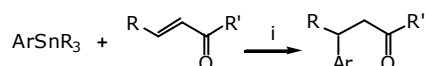
Scheme 4.1.4.7 - Attempted preparation of methyl tosylate salt **127**.

Following this, pyridinium salt **127** was prepared by modification of a literature reaction using excess methyl tosylate (which had been pre-treated with K₂CO₃ to remove any residual tosic acid). Polyvinylpyridine was used to scavenge the excess methyl tosylate and the product was isolated in 89% yield (**Scheme 4.1.4.8**).¹⁴¹



Scheme 4.1.4.8 - Preparation of methyl tosylate salt **127**.¹⁴¹

Unfortunately, this salt did not undergo rhodium catalysed 1,4-addition to methyl crotonate although there was no degradation of the starting materials. This situation remained unchanged even after 48 h (**Table 4.1.4.3, entry 2, pp 76**).



Reagents and conditions; (i) $[\text{Rh}(\text{COD})(\text{MeCN})_2]\text{BF}_4$,
THF, H_2O , 60 °C

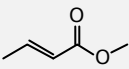
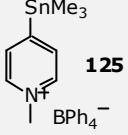
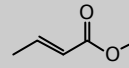
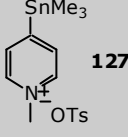
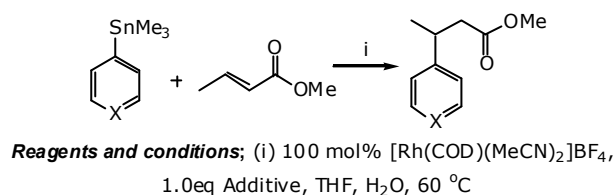
Entry	Substrate	ArSnR ₃	Outcome
1		 125	phenyl addition product 111
2		 127	-----

Table 4.1.4.3 – Summary of results for 1,4-addition reactions of arylstannane *N*-methyl pyridinium salts to methyl crotonate.

It appears that although the methyl tosylate ‘protection’ of the pyridine nitrogen is successful in so far as it prevents this substrate degrading under the reaction conditions, it renders the 4-position of the pyridyl ring unreactive towards 1,4-addition.

Having failed to induce a rhodium catalysed 1,4-addition reaction of the methyl tosylate pyridinium salt **127** to methyl crotonate it was decided to investigate stoichiometric rhodium promoted catalysed 1,4-addition reactions. This would eliminate any doubt that the catalytic reactions failed due to small amounts of ‘unprotected’ pyridine being present.¹⁴¹ Three parallel reactions were conducted (**Table 4.1.4.4, pp 77**). First, the reaction between phenyl trimethyl stannane and methyl crotonate was conducted with stoichiometric rhodium. This reaction proceeded to give the desired phenyl addition product in excellent yield as expected (i.e. a stoichiometric amount of catalyst does not hinder the 1,4-addition reaction) (**Table 4.1.4.4, entry 1, pp 77**). Second, the aforementioned reaction was spiked with one equivalent of the methyl tosylate pyridinium salt **127**. The methyl tosylate pyridinium salt **127** did not hinder the reaction, but did decompose under the reaction conditions (unlike when only 3 mol % of the rhodium catalyst was used) (**Table 4.1.4.4, entry 2, pp 77**). Finally, the 1,4-addition of the methyl tosylate pyridinium salt **127** to methyl crotonate was preformed. For the first time, the reaction showed trace formation of the desired 1,4-addition product by FAB-MS analysis, where the pyridyl cation of the desired salt was observed (**Table 4.1.4.4, entry 3, pp 77**).



Entry	ArSnR ₃	Additive	Outcome
1		-----	phenyl addition product 102
2			phenyl addition product 102
3		-----	evidence of trace amounts of the 1,4-addition product

Table 4.1.4.4 – A summary of stoichiometric rhodium catalysed 1,4-addition of aryl trimethylstannanes to methyl crotonate.

The results from the aforementioned studies suggested that counterion exchange between the rhodium complex **128** and the methyl tosylate pyridinium salt **127** might be taking place as depicted in Figure 4.1.4.1. This would explain why when a stoichiometric amount of the rhodium catalyst was used, degradation of the pyridinium salt was observed (i.e. formation of the methyl tetrafluoroborate pyridinium salt **119** which has been previously shown to undergo destannylation under these conditions driving the equilibrium to the right) (**Fig 4.1.4.1**).

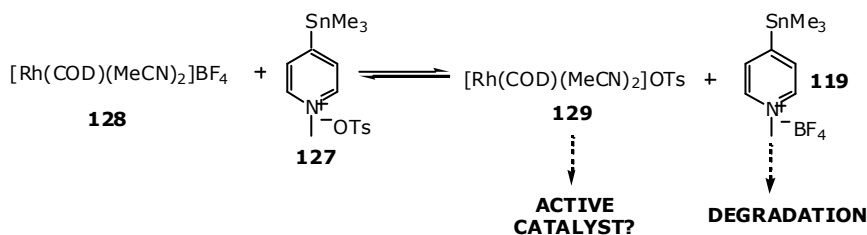
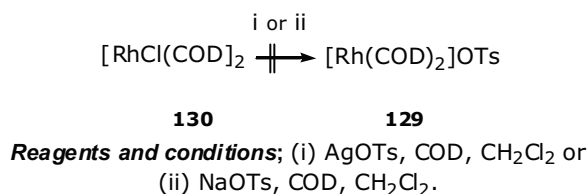


Figure 4.1.4.1 - Proposed equilibrium between rhodium complex **147** and pyridyl salt **145**.

However, with no insight into the position of the equilibrium it was decided to prepare rhodium complex **129** with the view to test this complex as a novel catalyst in the rhodium catalysed 1,4-addition reaction.

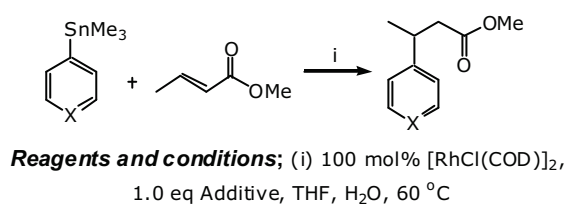
Efforts to prepare this catalyst through a modification of the method used to prepare the analogous complex **128** proved difficult. Rhodium complex **130** was

treated with silver tosylate and cyclooctadiene in CH_2Cl_2 but to our disappointment, none of the desired product was formed. Changing the reagent to sodium tosylate also failed to resolve the situation (**Scheme 4.1.4.9**).



Scheme 4.1.4.9 – Attempted Preparation of new $[\text{Rh}(\text{COD})_2]\text{OTs}$ **129** catalyst by reaction of rhodium dimer **130** with silver tosylate or sodium tosylate and cyclooctadiene.

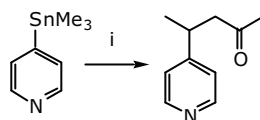
Due to the problems encountered with rhodium salts as catalysts in the 1,4-addition of 4-pyridyl stannane pyridinium salts to α,β -unsaturated esters we were interested to see whether substitution of the rhodium salts for a neutral rhodium complex would offer any advantages. Recent work by Furman showed that the success of the rhodium catalysed intramolecular 1,4-addition of vinylstannanes to 2,4-dihydro-4-pyridones was largely dependant on the nature of the catalyst employed.¹⁴⁶ Hence rhodium complex, $[\text{RhCl}(\text{COD})]_2$ was examined as the catalyst in this reaction. Two parallel reactions were carried out using a stoichiometric amount of $[\text{RhCl}(\text{COD})]_2$ complex (**Table 4.1.4.5**). First, the reaction between phenyl trimethyl stannane and methyl crotonate was attempted. The reaction was successful and thus tolerant of a stoichiometric amount of the $[\text{RhCl}(\text{COD})]_2$ complex (**Table 4.1.4.5, entry 1**). Second, the 1,4-addition of the 4-pyridyl trimethyl stannane methyl tosylate pyridinium salt **127** to methyl crotonate was attempted. Disappointingly, the reaction failed to give the desired 1,4-addition product (**Table 4.1.4.5, entry 2**).



Entry	ArSnR ₃	Outcome
1		phenyl addition product 102
2		no product/ degradation of the SM

Table 4.1.4.5 – 1,4-Addition reactions promoted by stoichiometric $[\text{RhCl}(\text{COD})]_2$.

Following our successful use of copper salts for the *in situ* protection of the pyridine nitrogen during copper catalysed 1,4-addition of pyridyl Grignard reagents to α,β -unsaturated ketones (see **4.4.2 Copper Catalysed Grignard 1,4-Additions**) attempts were made to 'dope' the rhodium catalysed 1,4-addition reaction of 4-pyridyl trimethyl stannane to penten-2-one with various copper salts, in the hope that the same effect would be observed here (**Table 4.1.4.6**).



Reagents and conditions; (i) Additive, THF, H₂O,
10 mol% [RhCOD(MeCN)₂]BF₄, 60 °C

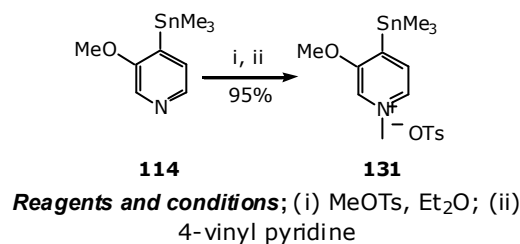
Entry	Additive	Outcome
1	CuI	no product/ degradation of the SM
2	CuBr.SMe ₂	no product/ degradation of the SM
3	CuClO ₄	no product/ degradation of the SM
4	CuBF ₄	no product/ degradation of the SM

Table 4.1.4.6 – Evaluation of copper salts in the copper catalysed 1,4-addition reaction.

Disappointingly, none of the desired 1,4-addition products were detected, and complete degradation of the stannane substrate was observed. Considering that the copper salts might not have fully dissolved in the reaction mixture it was decided to repeat the reactions dissolving the copper salts in dibutylsulfide prior to reaction. Again none of the desired products were observed.

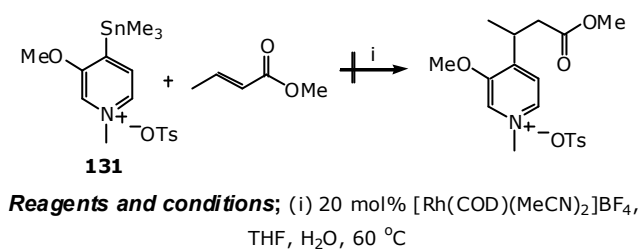
Finally, we decided to prepare the methyl tosylate pyridinium salt of 3-methoxy-4-pyridyl trimethyl stannane.

The preparation of this compound was achieved by using the same protocol for preparing the unsubstituted analogue, giving the required pyridinium salt **131** in excellent yield (95%) (**Scheme 4.1.4.10**).



Scheme 4.1.4.10 – Preparation of methyl tosylate pyridinium salt **131**.

To our disappointment, the reaction of this stannane with methyl crotonate failed to provide the desired product, even by FAB-MS analysis (**Scheme 4.1.4.11**).



Scheme 4.1.4.11 – Attempted 1,4-addition of methyl tosylate pyridinium salt **131** to methyl crotonate.

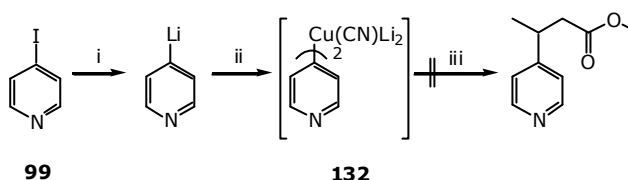
This substrate, being more electron-rich than the unsubstituted methyl tosylate pyridinium salt **127** (which did result in trace formation of the desired product) was expected to be more nucleophilic at the C4 position of the pyridine ring. However, perhaps the fact that the electron-donating group was in the *ortho*-position relative to the stannane made the position too sterically hindered.

At this juncture it was clear that finding conditions to allow the 1,4-addition of pyridyl metal reagents to enoates was proving more challenging than we had anticipated. It was apparent that the pyridine nitrogen lone pair was causing the reactions to fail but our strategies for negating this Lewis basic site were introducing additional complications either in the form of nucleophile counterions to salts and/or by making the pyridine ring too electron deficient to act as an effective nucleophile. Consequently, we decided to abandon the rhodium catalysed 1,4-addition strategy as a method for addition of pyridyl substrates to unsaturated systems.

Investigations into the utility of pyridyl copper reagents in 1,4-addition reactions; which had already been exploited in previous work by Nilsson and Mann were instigated.^{48,49,51}

4.2 Towards Evoninic Acid *via* Cuprate 1,4-Addition

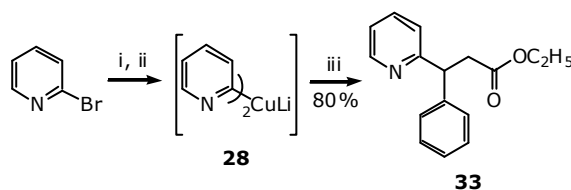
'Higher order cuprates' were chosen for initial investigation since they have been reported to be highly reactive in 1,4-addition transformations. Owing to the fact that 4-pyridyl cuprates are unprecedented in the literature, efforts to prepare a higher order 4-pyridyl cuprate **132**, using a modification of the procedure described by Mann⁵¹ for his 3-pyridyl cuprate, was attempted. Subsequent reaction of this cuprate with methyl crotonate gave disappointing results. First, we were not convinced that the cuprate had formed and second, in light of the low mass recovery of the reaction, alongside the absence of aromatic signals in the ¹H NMR, it was thought that perhaps pyridine was produced and thus lost during the course of the work-up (**Scheme 4.2.1.1**).



Reagents and conditions; (i) *n*-BuLi, THF, -78°C; (ii) CuCN; (iii) Methyl crotonate

Scheme 4.1.4.1– Attempted synthesis of a 4-pyridyl higher-order cuprate and its subsequent reaction with methyl crotonate.

Given these results, and the fact that the original reaction reported by Mann was using a more complex 3-pyridyl substrate, it was decided to first attempt to repeat Nilssons' 1,4-addition of the bis(2-pyridyl) Gilman cuprate **28** to ethyl *trans*-succinamate (**Scheme 4.2.1.2**).⁴⁸



Reagents and conditions; (i) *n*-BuLi, Et₂O, -78°C; (ii) CuI, SBU₂, Et₂O, 0 °C; (iii) Ethyl *trans*-succinamate, rt

Scheme 4.1.4.2 – Synthesis of the bis(2-pyridyl) Gilman cuprate **28** and its subsequent 1,4-addition to ethyl *trans*-cinnamate.

The reaction required rigorous drying of the glassware, purification of the reagents and rigorous exclusion of air and moisture in order to proceed efficiently. The 1,4-addition product, ester **33** was obtained in 80% yield (*cf.* lit: 82%).⁴⁸ In the absence of these precautions pyridine was formed as the major product.

It was decided to attempt to use this methodology for the first asymmetric synthesis of evoninic acid (**4**), and then to transfer the methodology to the C4-position on the pyridine ring (which to the best of our knowledge has not been previously reported), to give access to the 4-substituted pyridyl core required for the first synthesis of hydroxy *iso*-evoninic acid (**3**).

4.2.1 Unsubstituted 2-Pyridyl Cuprates

Our retrosynthetic analysis of evoninic acid is depicted below (**Fig 4.2.1.1**)

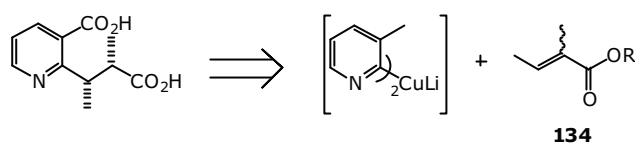
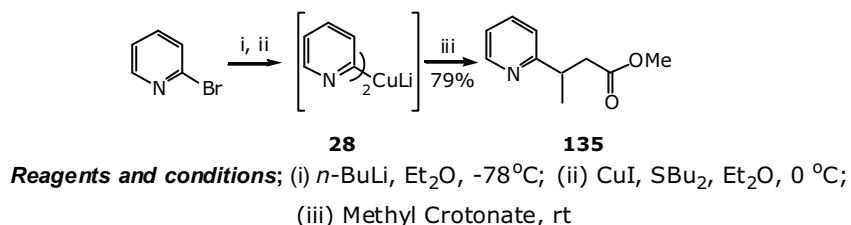


Figure 4.2.1.1 – Retrosynthetic analysis of evoninic acid.

Initial studies focused on exploring the scope of the cuprate 1,4-addition reaction with respect to the Michael acceptor particularly with respect to its tolerance of methyl groups at the α - and β -positions of enoates (e.g. **134**) (**Figure 4.2.1.1**).

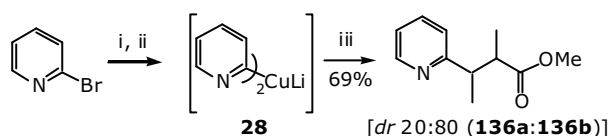
Substitution of ethyl *trans*-cinnamate for methyl crotonate was attempted first, where the β -carbon was now substituted with a methyl group (**Scheme 4.2.1.1**).



Scheme 4.2.1.1 – 1,4-Addition of the bis(2-pyridyl) Gilman cuprate to methyl crotonate.

The reaction proceeded smoothly to give the desired 1,4-addition product, ester **135** in good yield (79%).

Next, we were eager to see if the reaction was tolerant of substituents at both the α - and β -positions by substitution of methyl crotonate for methyl tiglate (**Scheme 4.2.1.2**).



Reagents and conditions; (i) *n*-BuLi, Et₂O, -78 °C; (ii) CuI, SBU₂, Et₂O, 0 °C; (iii) Methyl Tiglate, rt

Scheme 4.2.1.2 – 1,4-Addition of the bis(2-pyridyl) Gilman cuprate to methyl tiglate.

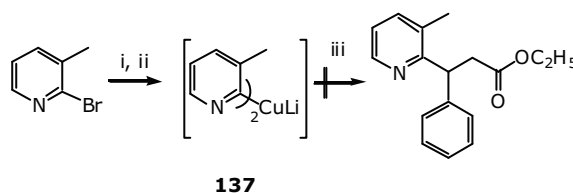
Encouragingly, the reaction furnished the desired product, ester **136** in 69% yield (*dr* 20:80, **136a**:**136b**),* which was surprising since α - and β -substituted α,β -unsaturated substrates are often inert to this type of reaction for steric reasons.

Encouraged by the initial success of these modifications, we decided to see if this chemistry could be further developed for the first synthesis of evoninic acid (**4**) and hopefully, the first synthesis of hydroxy *iso*-evoninic acid (**3**).

4.2.2 3-Substituted 2-Pyridyl Cuprates

We were anxious to see whether the reaction could tolerate a substituent at the C3 position of the pyridine ring, *ortho* to the cuprate (*N.B.* a carboxylic acid group at this position is required for the target molecule). *Ortho* substituents on aryl nucleophiles as previously discussed, are often not well tolerated in the 1,4-addition reaction due to the increase in steric bulk close to the reactive centre.

To probe this, we exposed 2-bromo-3-methyl pyridine to the Gilman cuprate forming conditions and reacted the resultant cuprate **137** to ethyl *trans*-cinnamate (**Scheme 4.2.2.1**).



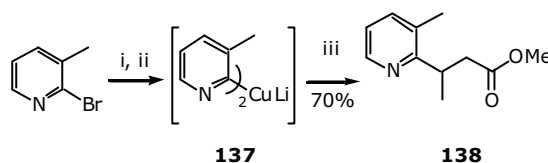
Reagents and conditions; (i) *n*-BuLi, Et₂O, -78 °C; (ii) CuI, SBU₂, Et₂O, 0 °C; (iii) Ethyl *trans*-cinnamate, rt

Scheme 4.2.2.1 - Preparation of the 3-methyl-2-pyridyl homo-cuprate **137** and attempted 1,4-addition to ethyl *trans* cinnamate.

To our disappointment, no evidence of the product was observed, only a mixture of the unsaturated substrate and 3-methyl pyridine was evident by ¹H NMR

* The diastereoisomers **136a** and **136b** were not assigned as syn/anti.

analysis. It appeared that an *ortho*-substituent might not be tolerated in the reaction. Since this was pre-requisite for our synthesis of evoninic acid. We decided to attempt the addition of the same cuprate **137** to methyl crotonate. This reaction proceeded to give the desired 1,4-addition product **138** in 70% yield (**Scheme 4.2.2.2**).

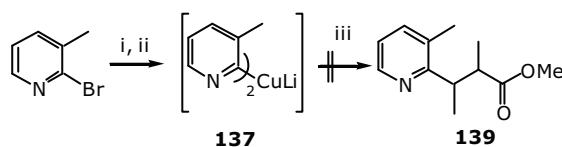


Reagents and conditions; (i) *n*-BuLi, Et₂O, -78°C; (ii) CuI, SBU₂, Et₂O, 0 °C;
(iii) Methyl crotonate, rt

Scheme 4.2.2.2 – 1,4-Addition reaction of the bis(3-methyl-2-pyridyl) Gilman cuprate **137** to methyl crotonate.

Clearly, a phenyl substituent on the β-carbon of the unsaturated substrate is not compatible with an *ortho*-substituted pyridyl cuprate, probably due to steric clashes of this group with the newly introduced methyl substituent at the C3 position of the pyridine ring.

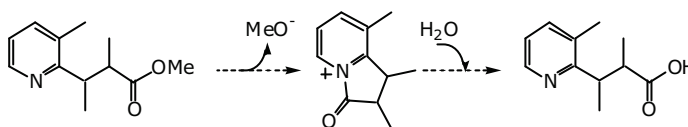
It remained for us to see if the *ortho*-substituted pyridyl cuprate was compatible with an α and β-substituted unsaturated substrate, by the 1,4-addition to methyl tiglate (**Scheme 4.2.2.3**).



Reagents and conditions; (i) *n*-BuLi, Et₂O, -78°C; (ii) CuI, SBU₂, Et₂O, 0 °C;
(iii) Methyl tiglate, rt

Scheme 4.2.2.3 – 1,4-Addition reaction of the bis(3-methyl-2-pyridyl) Gilman cuprate **137** with methyl tiglate.

Although the reaction proceeded to give trace amounts of the desired product by crude CI-MS and ¹H NMR analysis, we were unable to isolate sufficient quantities of the product to be synthetically useful. Purification by flash chromatography or reduced-pressure distillation was unsuccessful with the loss of the methoxy signal for the ester in the ¹H NMR. It was thought that hydrolysis of the ester was being facilitated by either an *inter*- or *intramolecular* interaction between the pyridine nitrogen and the carbonyl of the ester (**Scheme 4.2.2.4**).



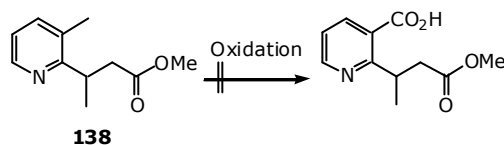
Scheme 4.2.2.4 - Postulated mechanism for *intramolecular* ester hydrolysis.

Prolonging the reaction times of the 1,4-addition using both methyl tiglate and methyl angelate (its stereoisomer) resulted in the successful isolation of the corresponding 1,4-addition product **139**, albeit in just 10 and 14% yields, respectively. Interestingly, we observed the opposite sense of diastereoselectivity depending on which stereoisomer of the unsaturated substrate used, the reaction with methyl angelate favoured the *syn* diastereoisomer (*dr* 63:37, **139s:139a**)* as required for the natural product evoninic acid (**Table 4.2.2.3, entries 1 & 2, pp 94**).

Given that we expected to be able to introduce a methyl group α to the ester in the methyl crotonate derived 1,4-addition product, ester **138** by alkylation, and also considering the high cost of methyl angelate, we did not pursue the use of methyl angelate further.

Our attention turned towards converting the benzylic methyl group to the corresponding carboxylic acid required for the target compound. The most obvious method was to perform an oxidation of the methyl group itself although we were mindful the alkyl substituent at the C2 position of the pyridine ring contains a benzylic methine proton that might also be prone to oxidation. Additionally, the pyridine nitrogen itself may also be problematic (*vis-a-vis* *N*-oxide formation) (**Table 4.2.2.1**).

* The diastereoisomers **139s** and **139a** were assigned following subsequent conversion of **139s** to evoninic acid (see **4.3.3 Diastereoselective Synthesis of ($\pm$)-Evoninic Acid**)

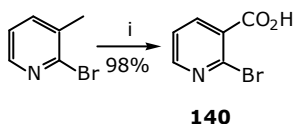


Entry	Conditions	Outcome
1	2.5 eq KMnO ₄ , H ₂ O, ? ¹⁴⁷	no product, evidence of hydrolysis of ester
2	5.0 eq KMnO ₄ , H ₂ O, ? ¹⁴⁷	no product/ degradation of starting material
3	CAN, 1,4-dioxane/H ₂ O, ?	no product, degradation of starting material
4	SeO ₂ , TBHP, 1,4-dioxane/H ₂ O, ? ¹⁴⁸	no product, degradation of starting material
5	KMnO ₄ , 18-Crown-6, benzene, ? ¹⁴⁹	no product, degradation of starting material

Table 4.2.2.1 - Attempted benzylic oxidation.

Initial attempts focused on the use of KMnO₄ as the oxidising agent in accord with the work of Ashimori, who described the use of this reagent to oxidise 2-bromo-3-methylpyridine to 2-bromonicotinic acid in good yield.¹⁵⁰ Analysis of the crude reaction mixture suggested that the KMnO₄ was being consumed but not apparently for the required oxidation (**Table 4.2.2.1, entry 1**). Increasing the number of equivalents of KMnO₄ had no desirable affect on the reaction, resulting in a mixture of unidentifiable products in the reaction mixture (**Table 4.2.2.1, entry 2**). Other oxidative methods were investigated, including non-aqueous conditions; however no suitable conditions could be identified to yield the desired oxidative product. Various conditions employed led to either extensive decomposition of starting materials or unidentifiable products (**Table 4.2.2.1, entries 3-5**).

Mindful that 2-bromo-3-methyl pyridine could be easily oxidised to the corresponding 2-bromonicotinic acid, we were intrigued by the possibility of using 2-bromonicotinic acid as a substrate in the 1,4-addition reaction. 2-Bromonicotinic acid **140** was prepared according to Ashimori's protocol to give the desired product in 98% yield (**Scheme 4.2.2.5**).¹⁴⁷



Reagents and conditions; (i) KMnO_4 , H_2O , $100\text{ }^\circ\text{C}$

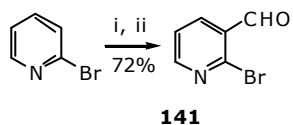
Scheme 4.2.2.5 – Benzylic oxidation of 2-bromo-3-methyl pyridine using potassium permanganate to give acid **140**.

Acid **140** was subjected to two equivalents of *n*-BuLi in Et_2O at $-78\text{ }^\circ\text{C}$ to prepare the *dilithio*-species. This was then immediately treated with copper iodide and dibutylsulfide to yield what we hoped would be the Gilman cuprate. However, on addition of methyl crotonate none of the desired 1,4-addition product was detected in the reactive mixture (**Table 4.2.2.3, entry 3, pp 94**). As copper is known to promote decarboxylation of aryl carboxylic acids this may have contributed to this failure.¹⁵¹

Owing to the lack of success in progressing the synthesis with a C3 methyl-substituent or a C3 carboxylic acid substituent on the pyridine ring, efforts were redirected to test the feasibility of varying the C3 substituent on the pyridine further.

Knochel has reported an elegant halogen-copper exchange reaction in the presence of various functional groups including aldehydes to prepare Gilman cuprates.¹⁵² Consequently, we decided to prepare the aldehyde at the C3 position on the pyridine ring, which we anticipated would be readily oxidised to the required carboxylic acid at a later stage in the synthesis.

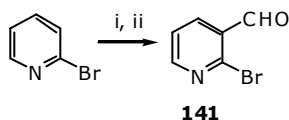
Aldehyde **141** was prepared by directed *ortho*-lithiation of 2-bromopyridine using LDA, in THF at $-78\text{ }^\circ\text{C}$ in 72% yield (**Scheme 4.2.2.6**).¹⁵³



Reagents and conditions; (i) LDA, THF, -78°C ; (ii) DMF

Scheme 4.2.2.6 – Directed *ortho*-lithiation of bromopyridine with LDA and quenching with DMF to afford aldehyde **141**.

Initial attempts to scale-up this reaction proved unsatisfactory (**Table 4.2.2.2**).



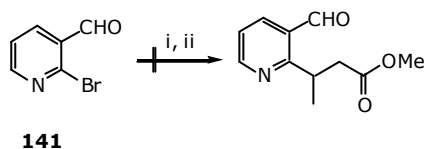
Reagents and conditions; (i) LDA, THF, -78°C ; (ii) DMF

Entry	Conc ⁿ LDA	Scale	Yield/%
1	0.4 M	0.20 g	72
2	0.4 M	2.00 g	22
3	1.0 M	1.00 g	35
4	1.5 M	1.00 g	28
5	2.0 M	1.00 g	20

Table 4.2.2.2 – Attempted optimisation of the DoM of 2-bromopyridine.

The concentration of LDA used was such that the amount of solvent required to conduct preparative work would have been unworkable. However, increasing the concentration of LDA had a detrimental effect on the yield (**Table 4.2.2.2, entries 2-5**).

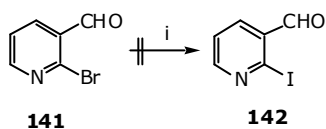
Despite these scale-up problems the halogen-copper exchange reaction was attempted using bromoaldehyde **141**. To a freshly prepared *neophyl* Gilman cuprate prepared according to the method of Knochel, from *neophyl*chloride and *tert*-butyllithium at -78°C , was added aldehyde **141** at -40°C , this was followed by the addition of the electrophile, methyl crotonate.¹⁵² Disappointingly, none of the desired 1,4-addition product was detected (**Scheme 4.2.2.7**).



Reagents and conditions; (i) (Neophyl)₂CuLi, Et₂O/THF, -40°C ;
(ii) Methyl crotonate

Scheme 4.2.2.7 - Attempted halogen-copper exchange of aldehyde **141** and subsequent 1,4-addition to methyl crotonate according to the method of Knochel.

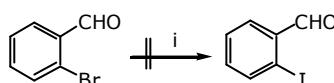
Although bromine-copper exchange was reported in the original paper, iodine-copper exchange was reported to be more efficient.¹⁵² In view of this, we decided to see whether we could replace the bromine with iodine in an aromatic Finkelstein reaction. The aldehyde **141** was treated with copper iodide, sodium iodide and *N,N'*-dimethylamine as the ligand according to the method of Buchwald (**Scheme 4.2.2.8**).¹⁵⁴



Reagents and conditions; (i) *N, N'*- Dimethylethylamine, NaI, CuI

Scheme 4.2.2.8 - Attempted aromatic Finkelstein reaction of bromoaldehyde **141** to form iodoaldehyde **142** according to the method of Buchwald.

However, on analysis of the crude reaction mixture by CI-MS, only the starting material was detected containing the signature bromine isotope pattern (^{79}Br : ^{81}Br , 1:1), indicating that no exchange had occurred. In the light of this result, the reaction was repeated in parallel with a test substrate: 2-bromobenzaldehyde (**Scheme 4.2.2.9**).¹⁵⁴



Reagents and conditions; (i) *N, N'*- Dimethylethylamine, NaI, CuI

Scheme 4.2.2.9 - Attempted aromatic Finkelstein reaction to convert 2-bromobenzaldehyde to 2-iodobenzaldehyde.

As evidenced by ^1H NMR and EI-MS analysis on the crude mixtures, both reactions were unsuccessful in yielding the desired products. We concluded that the *ortho* substituent was probably hindering the reaction from taking place as we noted that no *ortho*substituted cases were described in the original paper.¹⁵⁴

Continuing our search for a suitable substituent to occupy the C3 position on the pyridine ring, several candidate groups including a protected aldehyde, a nitrile, a vinyl group and a protected alcohol were considered.

Given the problems we were experiencing preparing the aldehyde **141** *via* the DoM route we devised a more efficient route to these substrates starting with 2-bromo-3-methyl pyridine (**Fig 4.2.2.1**).

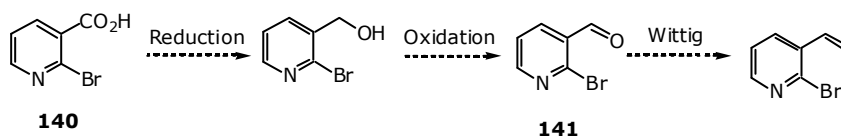
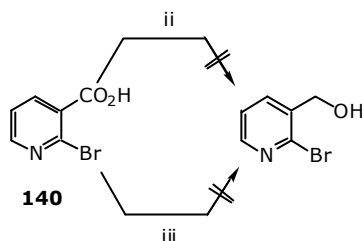


Figure 4.2.2.1 - Proposed synthesis of various C3 substituted pyridyl bromides.

This route was designed to give access to most of the substrates required for this study.

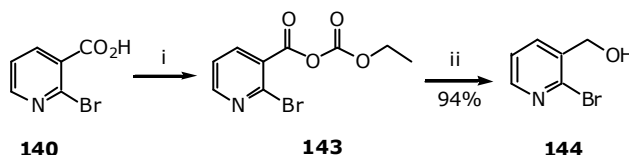
Attempts to reduce the carboxylic acid **140** to the corresponding alcohol with 'diborane' (a pre-mixed slurry of sodium borohydride and boron trifluoride etherate)¹⁵⁵ and with LAH were unsuccessful, resulting in the formation of several unidentifiable pyridine-containing products (**Scheme 4.2.2.10**).



Reagents and conditions; (i) NaBH₄, BF₃·OEt₂, 'B₂H₆';
(ii) LAH, Et₂O

Scheme 4.2.2.10– Attempted reduction of acid **140**.¹⁵⁵

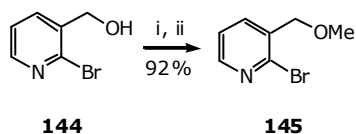
However, by preparing a mixed anhydride **143** of the acid with ethyl chloroformate followed by reduction with LAH, the desired alcohol **144** was formed in 94% yield (**Scheme 4.2.2.11**).¹⁵⁰



Reagents and conditions; (i) NEt₃, benzene, EtOC(O)Cl;
(ii) LAH, Et₂O, -78 °C, rt

Scheme 4.2.2.11 - Preparation of alcohol **144** via a mixed anhydride intermediate.¹⁵⁰

At this juncture we converted some of the alcohol **144** to the corresponding methyl ether **145** by reaction with NaH and MeI in 92% yield (**Scheme 4.2.2.12**).¹⁵⁶

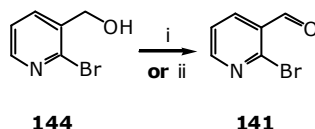


Reagents and conditions; (i) NaH, THF, 0 °C; (ii) MeI

Scheme 4.2.2.12 – Preparation of methyl ether **145**.¹⁵⁶

The 1,4-addition of the cuprate derived from methyl ether **145** to methyl crotonate gave a mixture of products. Purification by flash chromatography gave 50% starting material, 10% de-halogenated starting material and 10% of an unidentifiable pyridine-containing product, with data resembling that data expected for the desired 1,4-addition product but not conclusively and so this compound remained uncharacterised (**Table 4.2.2.3, entry 4, pp 94**).

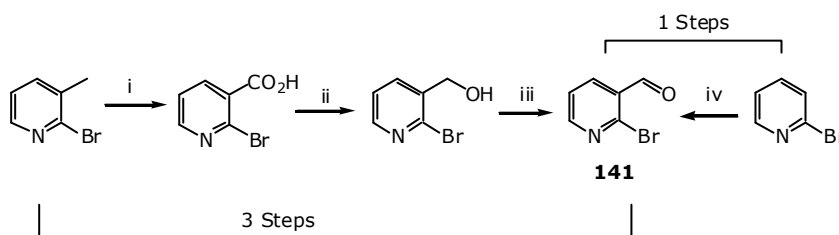
Oxidation of the pyridyl alcohol **144** to the corresponding aldehyde **141** was attempted using catalytic TPAP in the presence of NMO. This resulted in the formation of a 50:50 ratio of starting material and product. Disappointingly, on addition of a further 10 mol % of catalyst and 1 equivalent of NMO this ratio remained unchanged. Oxidation was subsequently achieved using a Moffats' oxidation with DCC, DMSO and anhydrous H_3PO_4 to give the desired, aldehyde **141** in excellent yield.¹⁵⁰ The TPAP conditions were not further optimised (**Scheme 4.2.2.13**).



Reagents and conditions; (i) TPAP, NMO, CH_2Cl_2 , 50:50 (SM:P);
(ii) DCC, DMSO, H_3PO_4 , 80%

Scheme 4.2.2.13 – Oxidation of alcohol **144** with TPAP and NMO.

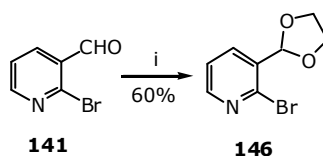
The overall yield for the preparation of aldehyde **141** *via* this route was significantly better than *via* to the DoM route (82%, 3 steps vs 40%, 1 step) (**Fig 4.6.2**).¹⁵³



Reagents and conditions; (i) KMnO_4 , H_2O , 100 °C; (ii) NEt_3 , EtOC(O)Cl , benzene; (iii) LDA, DMF, THF, -78 °C (iv) DCC, H_3PO_4 , DMSO

Figure 4.2.2.2 – Comparison of two routes leading to the formation of aldehyde **141**.

Aldehyde **141** was treated with ethylene glycol and PPTS in benzene to give dioxolane **146** in 60% yield (ca. 40% recovered starting material). A repeat of the reaction in the presence of 4 Å MS resulted in no measurable increase in the yield (**Scheme 4.2.2.14**).

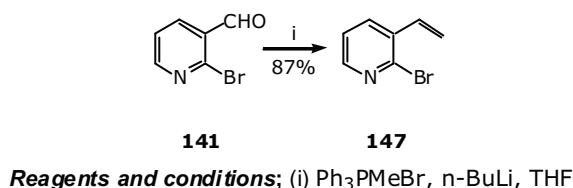


Reagents and conditions; (i) Ethylene Glycol, PPTS, Benzene

Scheme 4.2.2.14 - Protection of aldehyde **141** with ethylene glycol and PPTS to form dioxolane **146**.

1,4-Addition of the cuprate derived from dioxolane **146** to methyl crotonate gave just trace amounts of the desired product by crude CI-MS analysis, and we were unable to isolate the product pure (**Table 4.2.2.3, entry 5, pp 94**).

As a result, we directed our efforts to the preparation of the C3 vinyl pyridine. Vinyl pyridine **147** was prepared *via* a Wittig reaction with methyl phosphonium bromide salt in just 10% yield. The product was later found to be highly volatile, and consequent changes in the work-up procedures allowed us to isolate the desired vinyl pyridine **147** in 87% yield (**Scheme 4.2.2.15**).¹⁵⁷



Scheme 4.2.2.15 – Preparation of vinyl pyridine **147** by reaction of aldehyde **141** with methyl bromide phosphonium salt and *n*-BuLi.

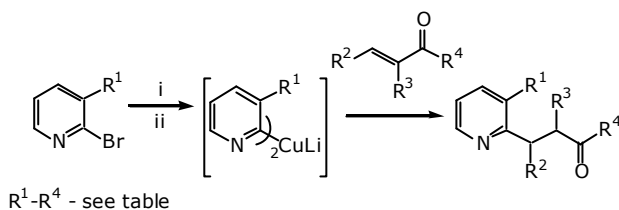
With 3-vinyl pyridine **147** in hand the 1,4-addition of the derived cuprate to methyl crotonate was attempted (**Table 4.2.2.3, entry 6, pp 94**). Once again, by crude analysis of the reaction mixture (¹H NMR and HRMS) we were able to detect the desired product, however the reaction was low yielding and isolation of the product proved impossible.

It was apparent from these investigations that the 1,4-addition reaction with pyridyl substrates substituted with groups at the C3 position on the pyridine ring other than methyl, were not well tolerated. Three reasons why this might be the case, were considered. First, the halogen-lithium exchange reaction might not be taking place. This idea was disproved by ¹H NMR analysis of the reaction mixtures; which identified the de-brominated starting materials as by-products in the reactions. Second, due to the steric demands of the newly introduced C3 substituents, the formation of the cuprate might be prevented. This argument falls down when you consider the size of the newly introduced groups relative to a methyl group (which appears not to disturb the course of the reaction). Third, perhaps efficient formation of the cuprate was possible, but stabilisation of the cuprate by the lone pairs on the newly introduced C3 appendages prevented the cuprate from reacting with the electrophile. This is probably the most plausible explanation because a vacant coordination site on the copper is believed to be required by the incoming electrophile in the 1,4-addition reaction to form the π -

complex prior to the oxidative addition to form the Cu(III) intermediate. Occupation of this vacant site would therefore cause the reaction to fail.

Having evaluated a number of 3-substituted-2-bromopyridine substrates in the 1,4-addition reaction to methyl crotonate with limited success, alternative Michael acceptors were evaluated. α,β -Unsaturated esters are known to be poor Michael acceptors relative to the corresponding ketones, nitriles and aldehydes, because the β -carbon is less electropositive. 1,4-Addition of the cuprate derived from both 2-bromopyridine and 2-bromo-3-methylpyridine to crotonaldehyde was attempted. Unfortunately, both reactions were unsuccessful (**Table 4.2.2.3, entry 7 & 8, pp 94**). This suggesting that α,β -unsaturated aldehydes were poor Michael acceptors for these particular substrates. Next, the 1,4-addition of the cuprates derived from both 2-bromopyridine and 2-bromo-3-methylpyridine to 3-pent-2-one was attempted. Encouragingly, both reactions proceeded to give the desired 1,4-addition products **148** and **149** in good yields (80 and 85% yields, respectively) (**Table 4.2.2.3, entries 9 & 10, pp 94**). Finally, the cuprate derived from 2-bromo-3-methylpyridine was added to crotononitrile. The reaction proceeded to furnish the desired product **150** in good yield (**Table 4.2.2.3, entry 11, pp 94**).

In general, it is clear that tolerance of substitution on the pyridine at C3 is very limited – the only successful cases of C3-substituted pyridine-derived cuprates undergoing 1,4-addition being those of the 2-bromo-3-methyl pyridine in combination with methyl crotonate, pentene-2-one, crotononitrile and less successfully with methyl tiglate and angelate. The failure of the cuprates containing groups other than methyl at the C3 position in the 1,4-addition addition reaction, despite extensive attempted optimisation of the conditions of the reaction, probably reflects either the co-ordinative stabilisation of these cuprates by the appendages or inadequate formation of the cuprate due to the high steric demands of these substrates.



Reagents and conditions; (i) *n*-BuLi, Et₂O, -78 °C; (ii) CuI, SBU₂, Et₂O, 0 °C

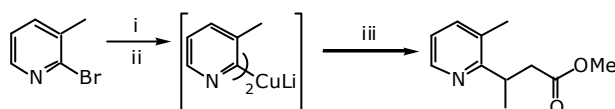
Entry	Substrate	Electrophile	Yield/%	<i>dr RR*:RS*</i>	Product
1			10%	27:77	 176
2			14%	33:67	 139
3	 140		-----	-----	
4	 145		trace	-----	
5	 146		trace	-----	
6	 147		trace	-----	
7			-----	-----	
8			-----	-----	
9			80%	-----	 148
10			85%	-----	 149
11			81%	-----	 150

Table 4.2.2.3 – 1,4-Addition of substituted and unsubstituted 2-pyridyl cuprates to electrophiles.

4.2.3 Optimization of Reaction Conditions.

As alluded to above, extensive efforts were made to optimise the 1,4-addition reaction conditions by investigating the variables relating to the formation and reactivity of the *ortho*-substituted pyridyl reagents. The reaction of 2-bromo-3-methyl pyridine with methyl crotonate was used for these studies.

Initial studies focused on the halogen-metal exchange step, by investigating the nature of the alkyllithium reagent (**Table 4.2.3.1**).



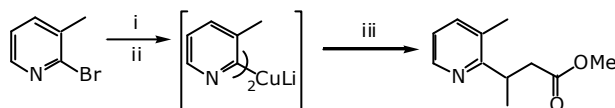
Reagents and conditions; (i) **Alkyl Lithium**, Et₂O, -78°C; (ii) CuI, SBut₂, Et₂O, 0 °C;
(iii) Methyl crotonate

Entry	Alkyl Lithium	Yield/%
1	<i>n</i> -BuLi	70
2	<i>sec</i> -BuLi	-----
3	<i>tert</i> -BuLi	23

Table 4.2.3.1 – The influence of alkyllithium reagent on 1,4-addition.

The standard reaction with *n*-BuLi gives the desired product in 70% yield (**Table 4.2.3.1, entry 1**). Surprising, the reaction using *sec*-BuLi gave none of the desired product (**Table 4.2.3.1, entry 2**). Finally, the reaction with *tert*-BuLi proceeded to give the desired product but with low conversion (23%) (**Table 4.2.3.1, entry 3**). It is apparent from these studies that the optimum alkyl lithium for the reaction is *n*-BuLi.

Next, the solvent and temperature were investigated (**Table 4.2.3.2**).



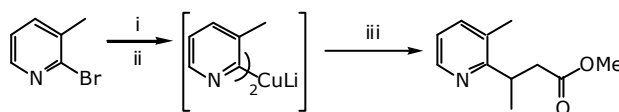
Reagents and conditions; (i) *n*-BuLi, **SOLVENT**, -78 °C; (ii) CuI, SBU₂, Et₂O, **TEMP/°C**;
(iii) Methyl crotonate

Entry	Solvent	Temp/°C	Yield/%
1	Et ₂ O	25	70
2	THF	25	trace
3	THF	60	----
4	DME	25	----
5	DME	50	----
6	1,4-dioxane	25	----
7	1,4-dioxane	100	----
8	CH ₂ Cl ₂	25	trace
9	CH ₂ Cl ₂ /Et ₂ O (50:50)	25	23

Table 4.2.3.2 – The influence of solvent and temperature on 1,4-addition.

The 1,4-addition of the cuprate of 2-bromo-3-methyl pyridine to methyl crotonate was conducted in THF, DME, 1,4-dioxane and also Et₂O–CH₂Cl₂ mixtures at both room temperature and at reflux (**Table 4.2.3.2, entries 1-8**). In all but one case no reaction took place, with only a low conversion in the case where an Et₂O–CH₂Cl₂ mixture was used (**Table 4.2.3.2, entry 9**). It appears that Et₂O is the optimum solvent for this reaction.

Finally, we investigated the influence of the nature of the copper salt on this reaction (**Table 4.2.3.3**).



Reagents and conditions; (i) *n*-BuLi, Et₂O, -78 °C; (ii) **COPPER SALT**, SBU₂, Et₂O, 0 °C;
(iii) Methyl crotonate

Entry	Copper Salt	Yield/%
1	CuI/SBU ₂	70
2	CuI.SMe ₂	60
3	CuBr.SMe ₂	20
4	CuCl/SBU ₂	----
5	CuCN/SBU ₂	----

Table 4.2.3.3 – The influence of the copper salt on 1,4-addition.

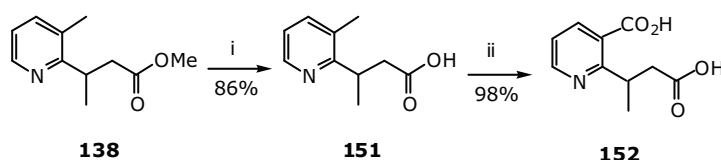
The results showed that SMe_2 exhibited no advantage over SBU_2 as the solubilising agent for the copper salt (**Table 4.2.3.3, entries 1 & 2**). Only one other salt examined, the $\text{CuBr} \cdot \text{SMe}_2$ complex, catalysed the reaction but gave low conversions (**Table 4.2.3.3, entry 3**). The remaining copper salts, i.e. CuCl and CuCN remained inert to the reaction conditions (**Table 4.2.3.3, entries 4 & 5**).

It was apparent from these studies that the optimum conditions for the 1,4-addition were those already being employed.

4.3 Synthesis of ($\pm$)-Evoninic Acid

4.3.1 Synthesis of the Model System

A re-investigation of the oxidation of the benzylic methyl group to the corresponding carboxylic acid was undertaken. The failure of previous attempts to effect this transformation can probably be attributed to the presence of the methyl ester group. It was thought that the oxidation conditions might have facilitated the hydrolysis of the methyl ester and the liberated methanol might have consumed the oxidising reagent to form methanoic acid. In light of this, methyl ester **138** was first hydrolysed (2N NaOH/MeOH) to give acid **151** (86%) and then subjected to oxidation conditions (KMnO_4). To our delight, the desired product **152** was furnished in excellent yield (98%) and with no evidence of *N*-oxidation (**Scheme 4.3.1.1**).



Reagents and conditions; (i) NaOH , MeOH , 67°C ; (ii) KMnO_4 , D_2O , 100°C , 14 h

Scheme 4.3.1.1 – Hydrolysis of ester **138** and oxidation to diacid **152** using KMnO_4 .

4.3.2 Diastereoselective Methylation

Following this, we now required an efficient method to install the remaining methyl group to furnish the natural product.¹⁵⁰ It was envisaged that installation of the methyl group could be achieved using ester **138** as the substrate. The results of this study are outlined below (**Table 4.3.2.1**).

Entry	Conditions	Yield/%	<i>dr</i> 139s: 139a*
1	LDA, -78 °C THF MeI, -40 °C, 1 h, rt	98	50:50
2	LDA, -78 °C THF MeI, -78 °C, 24 h	98	40:60
3	LDA, -78 °C Tol MeI, -40 °C, 1 h, rt	97	43:57
4	KHMDS, -78 °C, Tol MeI, -40 °C, 1 h, rt	96	89:11
5	KHMDS, -78 °C, Tol MeI, -78 °C, 24 h	98	96:4

* The diastereoisomers **139s** and **139a** were assigned following subsequent conversion of **139s** to evoninic acid (see **4.3.3 Diastereoselective Synthesis of (±)-Evoninic Acid**)

Table 4.3.2.1 – Alkylation of ester **138** to give methylated ester **139**.

Alkylation was readily achieved using LDA as the base followed by a MeI quench at -40 °C and immediately warming to room temperature.¹⁵⁸ This method allowed for the preparation of ester **139** in excellent yield but with no diastereoselectivity (**Table 4.3.2.1, entry 1**). Efforts focused on finding conditions that were selective for the formation of the *syn* diastereoisomer as required for the synthesis of the natural product. Initial attempts included leaving the reaction for a longer quench time of 24 h as opposed to 1 h and also lowering the temperature (-78 °C). Unfortunately, the selectivity was now slightly in favour of the unwanted *anti* diastereoisomer (**Table 4.3.2.1, entry 2**). Next we changed the solvent from THF to toluene, however this led to no improvement in the diastereoselectivity (**Table 4.3.2.1, entry 3**). Promisingly, a dramatic change in selectivity was observed when the base was changed from LDA to KHMDS. The product was isolated in excellent yield and now favouring the required *syn* diastereoisomer in a 87:13 ratio, (**139s:139a**) (**Table 4.3.2.1, entry 4**). This diastereoselectivity was further enhanced by reducing the temperature to -78 °C for 24 h, to give a 96:4 selectivity (**139s:139a**) as defined by ¹H NMR (**Table 4.3.2.1, entry 5**).

To explain the selectivity, we first assumed that the E(O)-enolate **153** of the ester was formed during the deprotonation with the amide base, since this minimises the 1,3-diaxial interactions in the 6-membered transition state for its formation (**Figure 4.3.2.2**).

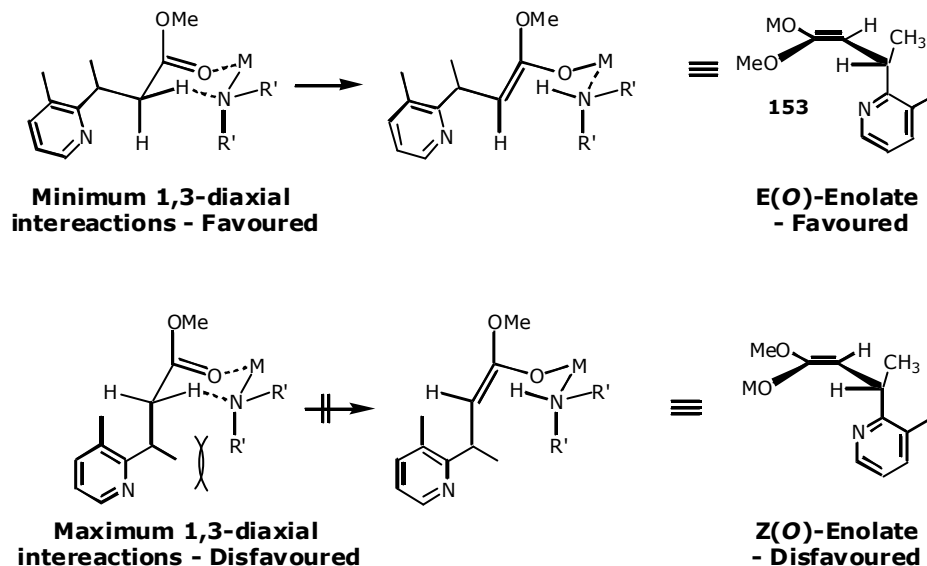


Figure 4.3.2.1 – Proposed 6-membered transitions states for enolate formation.

Next we considered two possible conformations for alkylation (**Figure 4.3.2.2**).

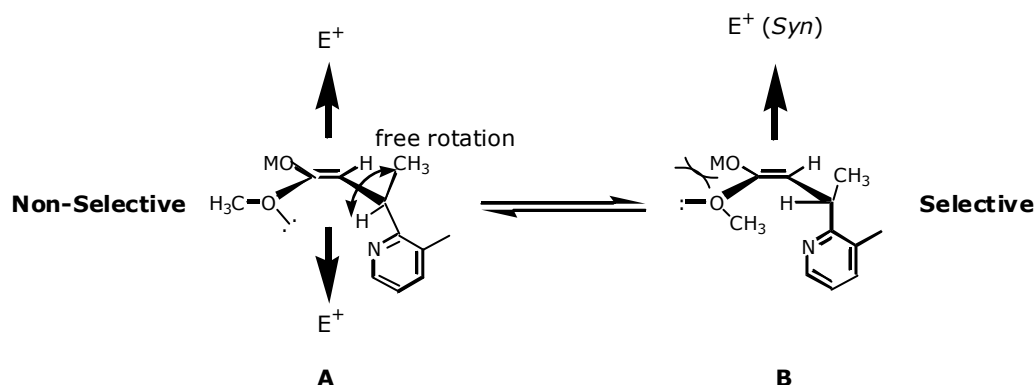


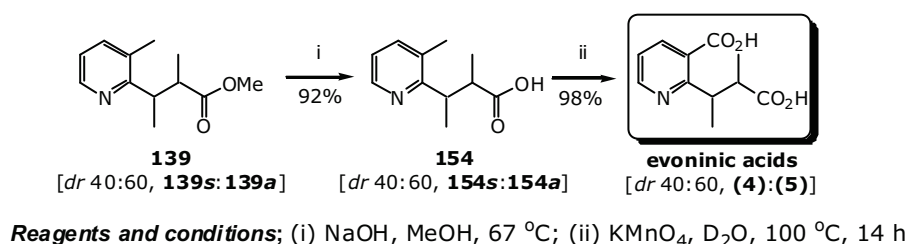
Figure 4.3.2.2 – Postulated conformations for selective and non-selective electrophilic addition.

If we first consider conformation **A**, where M is the lithium counterion, we know that addition of the electrophile occurs from both the top and bottom faces of the enolate unselectively. This is because the counterion is small so the methoxy group adopts the *s*-cis conformation. This places the oxygen lone pair as the group exerting steric control ($A^{1,3}$ -strain) over the rotation at the bond between C2 and C3. Since the lone pair is small, this control is poor and little selectivity is seen (**Figure 4.3.2.2**).

On the contrary, if we consider conformation **B**, where M is the potassium counterion, we know that the addition of the electrophile occurs exclusively from the top face of the enolate. This is because the counterion is now larger so the methoxy group adopts the *s*-trans conformation. This places the methoxy group as the group exerting steric control ($A^{1,3}$ -strain) at the bond between C2 and C3. This is more effective and so good control for attack by the electrophile on the opposite face to the pyridyl ring is seen (**Figure 4.3.2.2**).

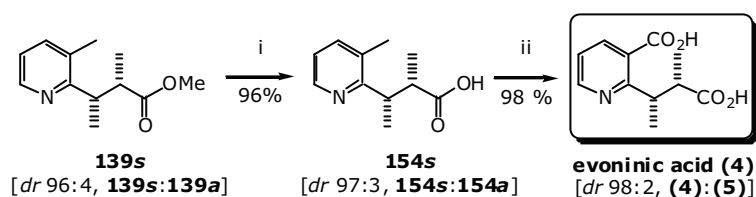
4.3.3 Diastereoselective Synthesis of (±)-Evoninic Acid

Following the successful diastereoselective installation of the methyl group, we were anxious to see if the hydrolysis and oxidation steps previously established in the model system would transfer to the actual system, whilst preserving the diastereochemical integrity of the molecule. First, a mixture of **139** (40:60, **139s:139a**) (**Table 4.3.2.1, entry 2**) was used to test the reactions on this new substrate. Compound **139** was treated with sodium hydroxide and subsequently oxidised with KMnO_4 to give evoninic acids (**4**) and (**5**) in excellent yield, and with no appreciable change in the diastereoselectivity set up in the alkylation reaction (**Scheme 4.3.3.1**)



Scheme 4.3.3.1 – Synthesis of evoninic acid (**4**) and *epi*-evoninic acids (**5**).

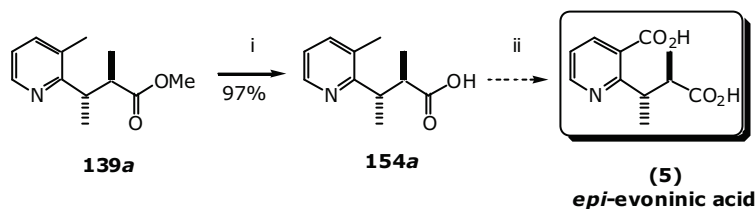
The diastereoisomerically highly enriched *syn* ester **139s** (*dr* 96:4 **154s:154a**, from **Table 4.3.2.1, entry 5**) also smoothly underwent hydrolysis (96% yield, *dr* 97:3 **154s:154a**) and subsequent oxidation to afford the desired natural product, evoninic acid (**4**) in 98% yield [*dr* 98:2 (**4**):(**5**)]. The *syn* stereochemistry was confirmed by comparison of the ^1H NMR coupling constants with those reported for the natural product (**Scheme 4.3.3.2**).²²



Reagents and conditions; (i) NaOH, MeOH, 67 °C; (ii) KMnO₄, D₂O, 100 °C, 14 h

Scheme 4.3.3.2 – Diastereoselective synthesis of evoninic acid (**4**).

The diastereomerically highly enriched anti ester **139a** [dr <1:99 **154s:154a**, obtained in 45% yield through repeated flash chromatography of the ester **139** from the reaction of ester **138** with LDA and MeI (**Table 4.3.2.1, entry 2**)] also underwent hydrolysis in excellent yield (97%, <1:99 **154s:154a**). However we were unable to complete the synthesis of *epi*-evoninic acid (**5**) due to insufficient material (**Scheme 4.3.3.3**).



Reagents and conditions; (i) NaOH, MeOH, 67 °C; (ii) KMnO₄, D₂O, 100 °C, o/n

Scheme 4.3.3.3 – Attempted synthesis of *epi*-evoninic acid (**5**).

In summary, the scope and limitations of 1,4-addition of 2-pyridyl Gilman homocuprates to enoates, first developed by Nilsson,⁴⁸ has been further explored with respect to tolerance of substitution at C3 of the pyridine ring and with respect to substituents at α and β of the enoate. As a result, the 1,4-addition of the cuprate derived from 2-bromo-3-methylpyridine to (*E*)-methyl crotonate has been employed as a key step in a highly diastereoselective synthesis of Celastraceae sesquiterpenoid constituent ($\pm$)-evoninic acid [4 steps, 64% yield overall *cf.* previous literature synthesis by Pailer and Pflieger 6 steps, <3% overall (see **2.1.3 Synthetic Precedent**)].²²

4.4 Enantioselective Synthesis of (-)-Evoninic Acid.

With a diastereoselective synthesis of ($\pm$)-evoninic acid in hand, we were now in a position to explore the development of an enantioselective synthesis. We envisaged three strategies to accomplish this. The first strategy, was to use a chiral auxiliary controlled 1,4-addition step. The second strategy was to develop new methodology based on Feringa's enantioselective copper catalysed Grignard

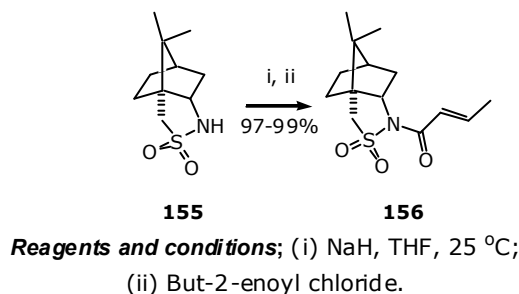
1,4-addition reaction.⁸⁵ The third strategy was to perform an enzymatic kinetic resolution of the racemate by hydrolysis. These three approaches are described below.

4.4.1 Chiral Auxiliary Controlled 1,4-Addition

There are numerous chiral auxiliaries¹¹¹ that could potentially be employed to control the stereochemical outcome of the 1,4-addition reaction. Two of the most widely documented acyl auxiliaries for 1,4-addition of Gilman cuprates are the camphor-based sultam and sulfonamide auxiliaries.^{107,108,110,159-164} These auxiliaries have been reported in the synthesis of many natural products and with a wide range of copper reagents.

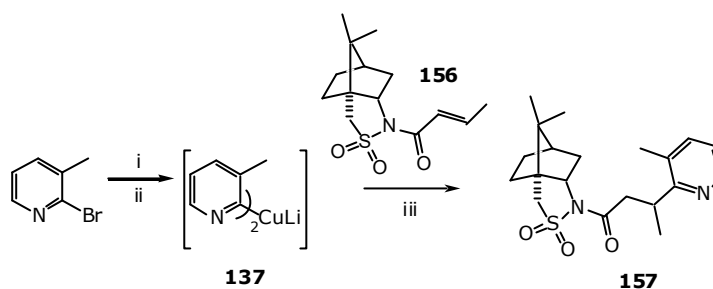
Prior to testing the 1,4-addition reaction, the chiral auxiliary had to be attached to the required enoate. Sultam **155** was treated with methyl crotonate and AlMe_3 in toluene and heated to reflux for 24 h, according to the procedure reported by Oppolzer but none of the required chiral enoate **156** was formed.¹⁵⁹

However, treatment of sultam **155** with NaH (60% in mineral oil) followed by butenoyl chloride in THF gave the desired chiral enoate **156** in excellent yields (97-99%) (**Scheme 4.4.1.1**).¹⁵⁹



Scheme 4.4.1.1- Preparation of chiral enoate **156**.

Our attempts at the 1,4-addition of the cuprate of 2-bromo-3-methyl pyridine **137** to chiral enoate **156** are summarised below (**Table 4.4.1.1**).



Reagents and conditions; (i) *n*-BuLi, **SOLVENT**, **TEMP/°C**;
(ii) CuI, SBU₂, 0 °C; (iii) Enoate **137**, **SOLVENT**, **TEMP/°C**.

Entry	Solvent	Temp/°C	Yield/%
1	Et ₂ O	25	-----
2	Toluene	-78	-----
3	Toluene	25	-----
4	Toluene/Et ₂ O	25	-----
5	CH ₂ Cl ₂ /Et ₂ O	25	28
6	CH ₂ Cl ₂ /Et ₂ O	-78	-----

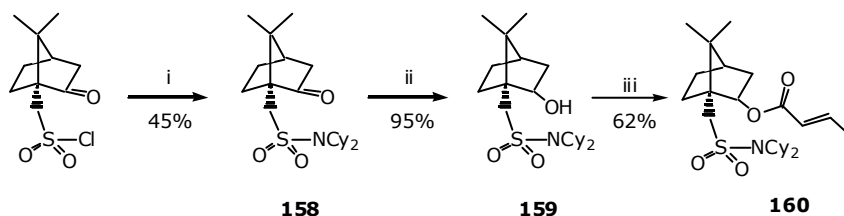
Table 4.4.1.1 – 1,4-Addition of the cuprate of 2-bromo-3-methyl pyridine **137** to chiral enoate **156**.

Initially we attempted to use those conditions previously established for the non-enantioselective reaction (i.e. the addition of the chiral enoate as a suspension in Et₂O at 25 °C) (**Table 4.4.1.1, entry 1**). Disappointingly, the reaction was unsuccessful. This may have been the expected result since the chiral enolate **156** was insoluble in Et₂O. Next, we attempted to use the conditions described by Oppolzer for their 1,4-addition reactions. The reaction was conducted in toluene at low temperature (-78 °C) (**Table 4.4.1.1, entry 2**).¹⁶² Again the reaction failed to provide the desired product. This was not too surprising since our pyridyl cuprates had previously been shown to be very unreactive at low temperature. The reaction was then conducted in toluene but now at room temperature (**Table 4.4.1.1, entry 3**). Disappointingly, the reaction again was unsuccessful in yielding the desired 1,4-addition product. Finally we decided to see if the reaction could be run in a mixed of solvent system i.e. by preparing the cuprate as before in Et₂O and then adding the chiral enoate in a solvent it was soluble in. Hence two reactions were run in parallel, one in an Et₂O/toluene mix (**Table 4.4.1.1, entry 4**) and the other in an Et₂O/CH₂Cl₂ mix (**Table 4.4.1.1, entry 5**). The reaction in CH₂Cl₂ gave the first 1,4-addition of our Gilman cuprate to a chiral enoate, albeit in low yield (28%). Disappointingly, no stereoinduction was observed, affording a mixture of diastereoisomers in *ca.* 1:1 ratio (*R,R*:*R,S*). We had feared that this might be the case since Oppolzer described how good stereoinduction was

generally only observed at low temperature ($-78\text{ }^{\circ}\text{C}$). Consequently, this 1,4-addition reaction was repeated at low temperature ($-78\text{ }^{\circ}\text{C}$) (**Table 4.4.1.1, entry 6**). However, at this low temperature no reaction was observed, with only the recovery of the starting material, chiral enoate **156**. It appeared that the pyridyl cuprate which was formed at $0\text{ }^{\circ}\text{C}$ and cooled to $-78\text{ }^{\circ}\text{C}$ prior to the reaction was completely insoluble below $0\text{ }^{\circ}\text{C}$ forming an insoluble gum at the bottom of the flask. This observation may account for the loss of reactivity at low temperature.

At this juncture we decided to prepare a chiral camphor sulfonamide auxiliary that Oppolzer reported as being effective for a range of asymmetric 1,4-addition reactions using Gilman cuprates.¹⁶⁵ We hoped that this auxiliary would provide some stereoselection at higher temperatures ($0\text{ }^{\circ}\text{C}$) considering the large steric bulk of the cyclohexane rings; which are reported to block one face of the enoate very effectively.

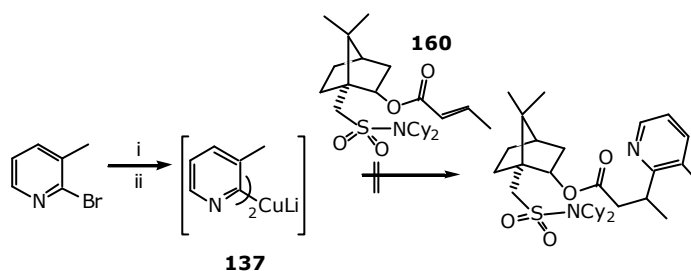
Camphor sulfonamide **158** was prepared from the corresponding camphor sulfonyl chloride *via* a standard addition elimination reaction with the corresponding amine, followed by reduction of the ketone to the alcohol **159** on reaction with L-Selectride™.¹⁶⁵ The chiral enoate **160** was then prepared by reaction of alcohol **159** with but-2-enoyl chloride and silver cyanide (**Scheme 4.4.1.2**).¹⁶⁶



Reagents and conditions; (i) DMAP, NEt_3 , MeCN, Cy_2NH ; (ii) L-Selectride, THF, $-78\text{ }^{\circ}\text{C}$; (iii) But-2-enoyl chloride, AgCN, benzene.

Scheme 4.4.1.2 – Preparation of chiral enoate **161**.

The cuprate of 2-bromo-3-methyl pyridine **137** was then treated with the chiral enoate **160** (**Table 4.4.1.2**).



Reagents and conditions; (i) *n*-BuLi, Et₂O, -78 °C;
(ii) CuI, SBU₂, **SOLVENT**, 25 °C.

Entry	Solvent	Yield
1	Et ₂ O	trace
2	CH ₂ Cl ₂	-----
2	toluene	-----

Table 4.4.1.2 – 1,4-Addition of the cuprate of 2-bromo-3-methyl pyridine **137** to chiral enoate **161**.

Initially the reaction was conducted in Et₂O at 25 °C but none of the desired product was observed (**Table 4.4.1.2, entry 1**). The 1,4-addition reaction was then repeated, again using a mixed solvent system (**Table 4.4.1.2, entry 2 & 3**). However, the reaction was unsuccessful in both toluene and CH₂Cl₂ mixtures with only quantitative recovery of starting material **160** being achieved.

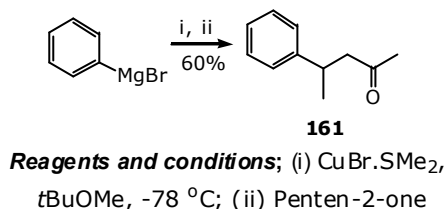
It appears from these results that a chiral auxiliary controlled 1,4-addition reaction is not compatible with our pyridyl Gilman cuprates. It is evident that not only are the reactions low yielding i.e. the Gilman cuprates are not as reactive to the chiral enoates relative the methyl crotonate, but also that the reactivity of the cuprates decreases significantly below 25 °C, a temperature not suitable for chiral induction using auxiliaries of this type. Following this, it was decided to put this strategy on hold and proceed with our second strategy, the copper catalysed Grignard 1,4-additions.

4.4.2 Copper Catalysed Grignard 1,4-Additions.

In 2004, Feringa reported the copper catalysed enantioselective 1,4-addition of Grignard reagents to acyclic enones.⁸⁵ In this communication they reported one example in which phenyl magnesium bromide reacted with penten-2-one with good conversion, regio-, and enantioselectivity [75%, 81:19 (1,4:1,2) and 76% e.e.]. Stereochemical control was achieved by using the ferrocenyl ligand either,

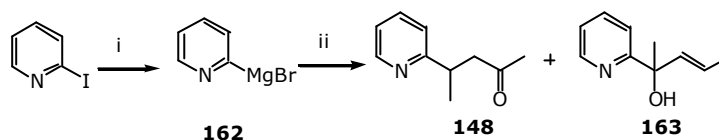
JosiPhos™ or TaniaPhos™ ligands in conjunction with copper bromide as catalyst in *t*BuOMe at low temperature (-75 °C).^{85 167}

As a prelude to our studies, we decided to repeat Feringa's reaction to see if we could duplicate his results (**Scheme 4.4.2.1**).⁸⁵



Scheme 4.4.2.1 – Copper-catalysed 1,4-addition of phenyl magnesium bromide to penten-2-one according to the method of Feringa.

The reaction between phenyl magnesium bromide to penten-2-one proceeded with excellent conversion, however not with complete regioselectivity. We obtained both the undesired 1,2-addition product and the desired 1,4-addition product **161** in a 1:2 ratio by ¹H NMR.⁸⁵ Despite this result we attempted to transfer the methodology to an unsubstituted 2-pyridyl substrate. This proved challenging; our results are summarised below (**Table 4.4.2.1**).

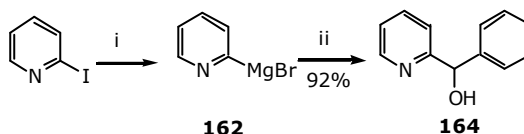


Reagents and conditions; (i) EtMgBr, Et₂O, rt; (ii) X mol% CuBr.SMe₂, tBuOMe, Y °C; (iii) Penten-2-one

Entry	Conditions	Conversion	148:163
1	5 mol %CuBr.SMe ₂ , 6 mol % TaniaPhos, -78 °C	-----	-----
2	100 mol %CuBr.SMe ₂ , -78 °C	-----	-----
3	200 mol %CuBr.SMe ₂ , -78 °C	83%	100:0
4	150 mol %CuBr.SMe ₂ , -78 °C	90%	100:0
5	110 mol %CuBr.SMe ₂ , -78 °C	87%	100:0
6	110 mol %CuBr.SMe ₂ , 0 °C	57%	60:40
7	110 mol %CuBr.SMe ₂ , 20 °C	78%	58:42

Table 4.4.2.1 - Catalytic loading studies on the copper-catalysed 1,4-addition of the 2-pyridyl Grignard reagent to penten-2-one.

In parallel with all these reactions, a control reaction was conducted to ensure the complete formation of the pyridyl Grignard reagent. Thus the pyridyl Grignard reagent **162** was added to benzaldehyde to give alcohol **164** in 92% yield (**Scheme 4.4.2.2**).¹⁶⁸



Reagents and conditions; (i) EtMgBr, Et₂O, rt; (ii) Benzaldehyde

Scheme 4.4.2.2 – Control Reaction - Iodine-magnesium exchange reaction followed by benzaldehyde quench.

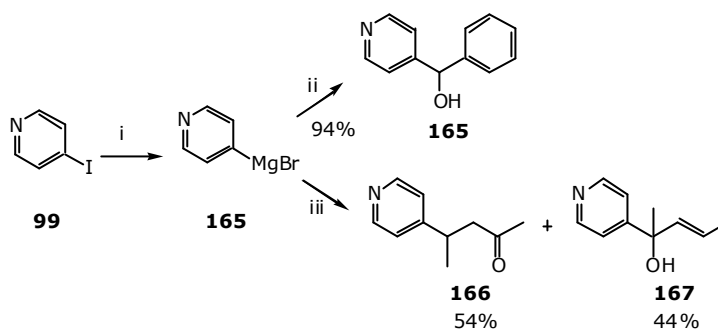
The copper catalysed 1,4-addition reaction of 2-pyridyl magnesium bromide using catalytic CuBr.SMe₂, tBuOMe and penten-2-one at -75 °C for 2 h yielded none of the desired 1,4-addition or even the undesired 1,2-addition products. Considerable loss of mass in the crude reaction mixture was however observed (**Table 4.4.2.1, entry 1**). Increasing the catalytic loading of CuBr.SMe₂ from 5 to 100 mol% saw no improvement in the reaction (**Table 4.4.2.1, entry 2**).

Surprisingly, using 200 mol% of catalyst resulted in complete conversion and exclusive formation of the desired 1,4-addition product, ketone **163** in excellent yield (**Table 4.4.2.1, entry 3**). Subsequent studies showed that the catalytic loading could be reduced from 200 to 150 mol% (**Table 4.4.2.1, entry 4**) and further still to 110 mol% whilst still giving exclusive formation of the 1,4-addition product **163** in high yields (**Table 4.4.2.1, entry 5**). Increasing the temperature to 0 °C (**Table 4.4.2.1, entry 6**) and 25 °C (**Table 4.4.2.1, entry 7**) saw the loss of regioselectivity, giving equal amounts of the 1,4- **148** and 1,2- **163** addition products in high conversion.

These studies show that it is essential that greater than one equivalent of the catalyst (copper bromide) is required to allow the reaction to take place, however if exactly one equivalent of the catalyst is used, no reaction is observed. These results suggest that one equivalent of the copper bromide is required to protect/block the pyridine nitrogen, allowing the remainder of the copper to catalyse the 1,4-addition reaction.

We next attempted to conduct the reaction in the presence of 5 mol% of the chiral JosiPhos™ ligand using 110 mol% of the CuBr.SMe₂. The 2-pyridyl Grignard reagent was pre-mixed with exactly one equivalent of the copper bromide, prior to its addition to the catalytic 1,4-addition reaction conditions. The reaction proceeded efficiently in excellent yield, however the reaction displayed no stereochemical control as determined by chiral GC analysis, where both enantiomers were present in equal amounts. This was most probably due to the large excess of copper bromide in the reaction where ligand exchange between the copper centres is probable.

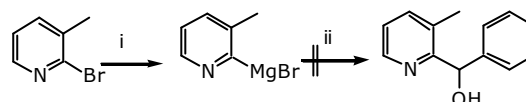
Attempts to transfer the methodology to the C4-position on pyridine ring (*i.e.* using 4-iodopyridine) showed promising results. Initially, as before, a control reaction with benzaldehyde gave alcohol **165** in 94% yield. Subsequent addition of the Grignard reagent to penten-2-one at 25 °C occurred in high conversion but displayed no regioselectivity, giving the 1,4-addition product **166** and the 1,2-addition product **167** in equal amounts (**Scheme 4.4.2.3**).



Reagents and conditions; (i) EtMgBr, Et₂O, rt; (ii) EtMgBr, Et₂O, rt, benzaldehyde; (iii) 200 mol% CuBr.SMe₂, tBuOMe, -78-25 °C, Penten-2-one

Scheme 4.4.2.3 - Copper-catalysed reaction of the 4-pyridyl Grignard reagent with penten-2-one.

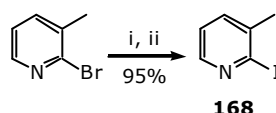
Attempts were made to prepare the Grignard reagent of 2-bromo-3-methyl pyridine *via* the same halogen-magnesium exchange protocol. Disappointingly, the reaction was unsuccessful, possibly due to steric hindrance of the *ortho*-substituent (**Scheme 4.4.2.4**).



Reagents and conditions; (i) EtMgBr, Et₂O, rt; (ii) Benzaldehyde

Scheme 4.4.2.4 – Attempted halogen-magnesium exchange of 2-bromo-3-methyl pyridine followed by quench with benzaldehyde.

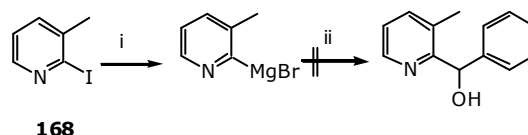
Since halogen-magnesium exchange reactions are often best preformed using iodides, preparation of 2-iodo-3-methyl pyridine **168** was undertaken. 2-Bromo-3-methyl pyridine was treated with *n*-BuLi and quenched with 1,2-diiodoethane to give the iodide **168** in excellent yield (**Scheme 4.4.2.5**).



Reagents and conditions; (i) *n*-BuLi, THF, -78 °C; (ii) ICH₂CH₂I

Scheme 4.4.2.5 – Synthesis of 2-iodo-3-methyl pyridine **168**.

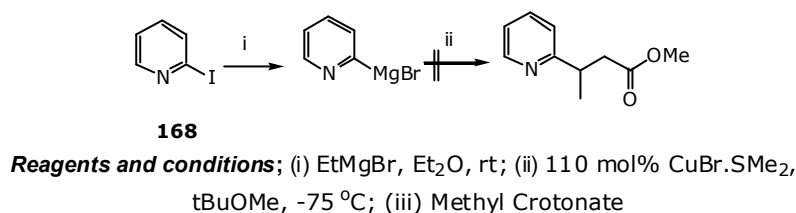
Attempted halogen-magnesium exchange on iodide **168** with ethyl magnesium bromide was unsuccessful as evident from its failure to participate in 1,2-addition to benzaldehyde (**Scheme 4.4.2.6**).



Reagents and conditions; (i) EtMgBr, Et₂O, rt; (ii) Benzaldehyde

Scheme 4.4.2.6– Attempted iodine-magnesium exchange of iodide **168** and quench with benzaldehyde.

Finally, we decided to attempt the 1,4-addition reaction of the unsubstituted 2-pyridyl Grignard reagent with methyl crotonate using the optimum conditions (**Scheme 4.4.2.7**).



Scheme 4.4.2.7 – Attempted copper catalysed 1,4-addition of 2-pyridyl-3-methyl magnesium bromide to methyl crotonate.

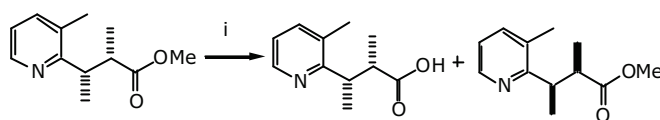
Disappointingly, the reaction was unsuccessful at both low temperature (-78 °C) and at high temperature (25 °C).

Owing to the unsuccessful enantioselective copper catalysed 1,4-addition of the 2-pyridyl-3-methyl magnesium bromide to penten-2-one and the unsuccessful addition to methyl crotonate this strategy was unlikely to provide the solution to our problem and was thus abandoned.

4.4.3 Enzymatic Resolution

Our final strategy for the development of an enantioselective synthesis of (-)-evoninic acid was to use an enzymatic hydrolysis to effect a kinetic resolution *en route*. The plan was to achieve the kinetic resolution immediately following the ester methylation step using the diastereomerically enriched *syn* isomer **139s** as the substrate. Since the hydrolysis of this compound is required anyway prior to oxidation the enzymatic hydrolysis would not increase the step count.

Seven enzymes were surveyed, the enzymes were incubated in acetone and water at 25 °C before the addition of the ester (**Table 4.4.3.1**).

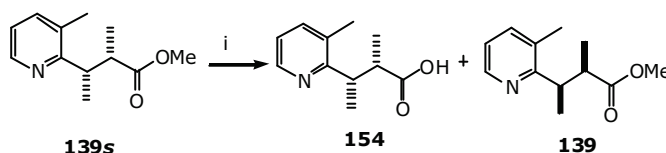
**139s****Reagents and conditions;** (i) Enzyme, acetone, H₂O

Entry	Enzyme	Outcome SM:P
1	Lipase	SM
2	Pig Liver Esterase (immobilised)	SM
3	Lipase P. Fluorescens	75:25
4	Lipase P. Cepacia	SM
5	α -Chymotrypsin	91:9
6	Pig Liver Esterase	91:9
7	Novocym	SM

Table 4.4.3.1 - Attempted enzymatic resolution of ester **139s** in acetone/water.

Three of the seven enzymes studied showed interesting results: lipase P. fluorescens, α -chymotrypsin and pig liver esterase showed evidence of hydrolysis taking place, but complete reaction was not observed (**Table 4.4.3.1, entries 3, 5 & 6**).

Attempts were made to optimise the reaction conditions for these three enzymes by incubating the enzymes in a potassium phosphate pH 7.0 buffer at 37 °C (**Table 4.4.3.2**).

**139s****154****139****Reagents and conditions;** (i) Enzyme, Ph 7.0 phosphate buffer

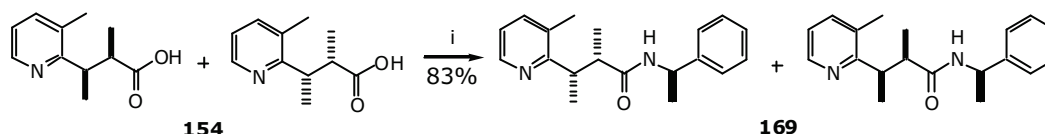
Entry	Enzyme	Solvent SM:P
1	Lipase P. Fluorescens	50:50
2	α -Chymotrypsin	racemization of SM <i>dr</i> 96:4 – 80:20
3	Pig Liver Esterase	0:100

Table 4.4.3.2- Attempted enzymatic resolution of ester **139s** using a pH 7.0 buffer at 37 °C.

The most promising result was seen in the case of the lipase P. fluorescens. The ¹H NMR indicated a 1:1 ratio of the ester and the acid suggesting the possible occurrence of an enantioselective hydrolysis reaction. (**Table 4.4.3.2, entry 1**). In the case of the α -chymotrypsin we saw racemization of the starting material (*dr* 96:4 → 80:20 **139s**: **139a**) (**Table 4.4.3.2, entry 2**). In the case of pig liver esterase we saw complete hydrolysis of both enantiomers of the ester to the acid (**Table 4.4.3.2, entry 3**).

To establish whether the lipase P. fluorescens hydrolysis reaction had effected a resolution of the enantiomers of ester **139s**, it was planned to derivatise the acid **154** obtained from the enzymatic hydrolysis reaction with (*R*)- α -methylbenzylamine. We were able to separate the ester from the acid by partitioning between H₂O and Et₂O.

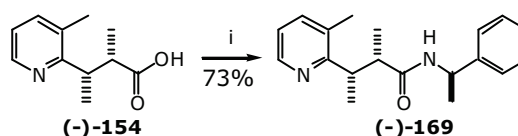
As a prelude to this, racemic acid **154** was derivatised with commercial (*R*)- α -methylbenzylamine using Mukaiyama's coupling reagent. The desired amides were obtained as expected as a 50:50 mixture of diastereoisomers **169a** and **169b** in good yields (**Scheme 4.4.3.1**).



Reagents and conditions; (i) 2-Chloropyridine-*N*-methyl iodide pyridinium salt, CH₂Cl₂
(ii) (*R*)-benzylamine, Et₃N and CH₂Cl₂.

Scheme 4.4.3.1 – Derivatisation of racemic acid **154** with (*R*)- α -methylbenzylamine.

Following this, we proceeded to derivatise acid (*-*)-**154** from the enzyme hydrolysis reaction with (*R*)- α -methylbenzylamine (**Scheme 4.4.3.2**).



Reagents and conditions; (i) 2-Chloropyridine-*N*-methyl iodide pyridinium salt, CH₂Cl₂
(ii) (*R*)-benzylamine, Et₃N and CH₂Cl₂.

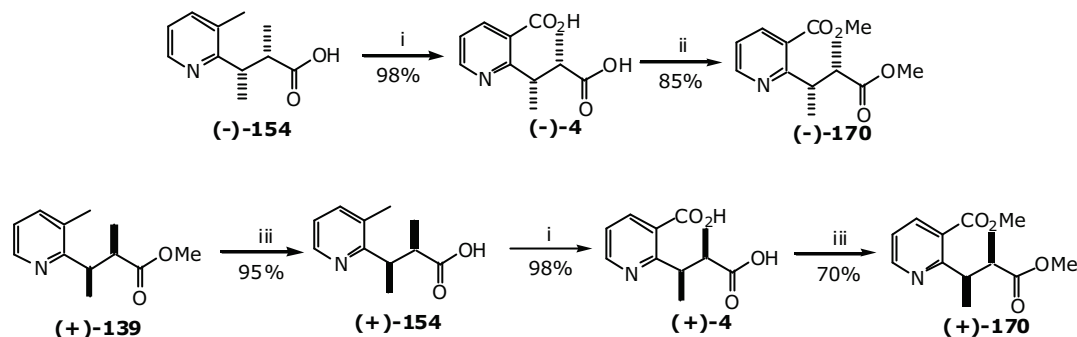
Scheme 4.4.3.2 – Derivatisation of acid (*-*)-**154** with (*R*)- α -methylbenzylamine.

Analysis of both the ¹H and ¹³C NMR spectra of the crude product of this reaction showed the presence of just a single diastereoisomer (*dr* > 95:5, [α]_D²⁰ = -78). This confirmed that the enzymatic hydrolysis had been successful in resolving the enantiomers of the ester – only hydrolysing one enantiomer to the acid and leaving the other enantiomer as the ester. It was now necessary to establish the absolute configuration of this acid (*-*)-**154**, which had a specific optical rotation of [α]_D²⁰ = -31.9.

4.4.4 Enantioselective Synthesis of (*-*)-Evoninic Acid

Having established the enantiopurity of the acid (*-*)-**154** both this compound and the methyl ester of its enantiomer [i.e. (*+*)-**139**] from the enzymatic kinetic resolution reaction were converted into the two enantiomers of evoninic acid (**4**)

separately. The literature optical rotation data for natural evoninic acid was in fact recorded on its methyl ester derivative^{10,13,14} so both products were treated with trimethylsilyldiazomethane in MeOH for 4 h to give the corresponding dimethyl evoninate enantiomers (**Scheme 4.4.4.1**).



Reagents and conditions; (i) KMnO_4 , H_2O , reflux; (ii) TMSCHN_2 , MeOH;
(iii) NaOH , MeOH, reflux,

Scheme 4.4.4.1 – Preparation of (-)-evoninic acids **(-)-4** and **(+)-4** and of their dimethyl esters **(-)-170** and **(+)-170**.

The specific optical rotation for the dimethyl ester prepared from the acid **(-)-154** was found to be $[\alpha]_{\text{D}}^{20} -41.2$ (CHCl_3), which compares well to that reported for natural (-)-evoninic acid dimethyl ester, $[\alpha]_{\text{D}}^{20} -42$ (CHCl_3).¹⁴¹⁵ Its enantiomer, gratifyingly, had an equal and opposite optical rotation $\{[\alpha]_{\text{D}}^{20} +43.3$ (CHCl_3)}. It is clear from these results that the evoninic acid prepared from the acid in the enzymatic resolution reaction is identical to the natural product. To the best of our knowledge this is the first asymmetric synthesis of (-)-evoninic acid.

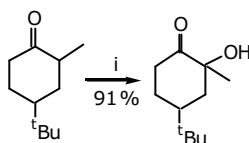
4.5 Synthesis of the Hydroxy Evoninic acid

With regards to our synthetic strategy for the synthesis of hydroxy *iso*-evoninic acid, an electrophilic oxidation step is required to build the quaternary carbon centre by the installation of a hydroxyl group α to the aliphatic carboxylic acid. In order to establish the conditions for this step prior to embarking on the synthesis of this natural product, we considered using ester **139** from the synthesis of (-)-evoninic acid as a model system, with the view to initially prepare the un-natural product hydroxy evoninic acid. The following section describes this work.

4.5.1 α -Hydroxylation Reactions

A survey of the literature revealed a number of different methods for the α -hydroxylation of carbonyl compounds. The following summary is not exhaustive but limited to cases relevant for our synthesis: i.e. those with tetra-substituted enolates, those involving esters and those having asymmetric variants.

The use of tetra-substituted enolates in α -hydroxylation reactions is limited to only a few examples. Aube described the α -hydroxylation of a cyclic ketone *via* a tetra-substituted enolate using a $\text{HN}(\text{TMS})_2$ -TMSI followed by oxidation with *m*CPBA as the oxidant (**Scheme 4.5.1.3**).¹⁶⁹

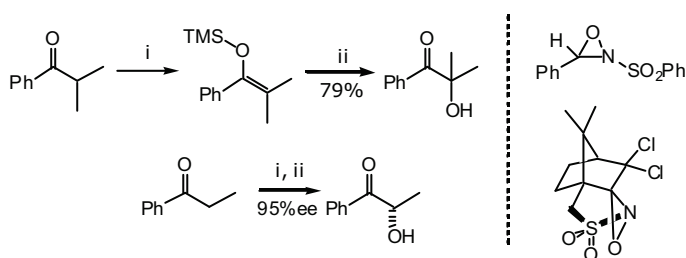


Reagents and conditions; (i) $\text{HN}(\text{SiMe}_3)_2$ -TMSI; (ii) *m*CPBA; $n\text{Bu}_4\text{NF}$

Scheme 4.5.1.1 – Aube's α -hydroxylation of tetrasubstituted enolate with *m*CPBA.

The reaction proceeded to give the product in excellent yield, however no asymmetric version was disclosed.

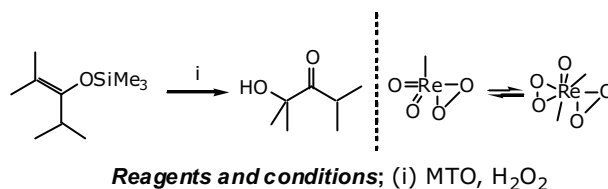
Davis developed the oxidation of silyl enol ethers using 2-(phenylsulfonyl)-3-phenyl oxaziridine in good yields. However, the use of a chiral oxaziridine gave poor asymmetric induction (i.e. e.e.'s of between 7.5 and 11%). Later, Davis reported a much improved asymmetric version using 8,8-(dichlorocamphoryl)sulfonyloxaziridine as the oxidant and obtained high stereoinduction in certain cases (e.g. 95% e.e. in the reaction shown below) (**Scheme 4.5.1.1**).¹⁷⁰



Reagents and conditions; (i) Base, TMSCl; (ii) Oxaziridine, CHCl_3 , 25 °C, Bu_4NF , THF

Scheme 4.5.1.2 – Davis' oxidation of silyl enol ethers with achiral and chiral oxaziridines.

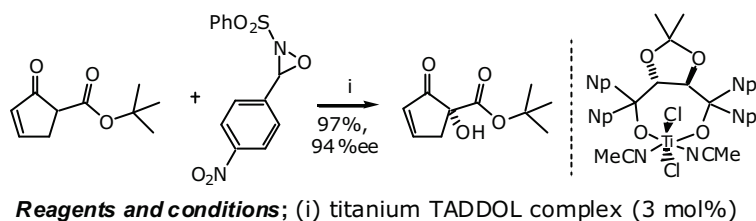
Espenson, disclosed the use of methyltrioxorhenium, CH_3ReO_3 (MTO) in the oxidation of tetrasubstituted silyl enol ethers using H_2O_2 as the oxidant in excellent yield (**Scheme 4.5.1.2**).¹⁷¹



Scheme 4.5.1.3 – Espenson's oxidation of tetra-substituted silyl enol ethers with MTO and H₂O₂.

Chiral rhenium oxo complexes have not yet been described for this type of transformation.

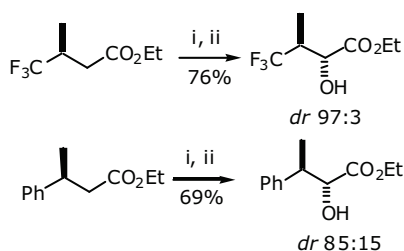
The first enantioselective α -hydroxylation of a tetrasubstituted β -keto ester using an oxaziridine as the oxidant, catalysed by a chiral titanium TADDOL complex was reported by Togni (**Scheme 4.5.1.5**).^{172,173}



Scheme 4.5.1.4 – Togni's enantioselective α -hydroxylation of a β -keto esters.

The reaction proceeded to give the α -hydroxy product in excellent yield and enantioselectivity.

Finally, Morizaiva described the synthesis of an α -hydroxyl, β -trifluoromethyl ester in high diastereoselectivity using Vedejs' reagent, MoO₅-pyridine-HMPA.¹⁷⁴ The selective hydroxylation of the non-fluorinated compound was also reported, albeit with lower selectivity (**Scheme 4.5.1.5**).



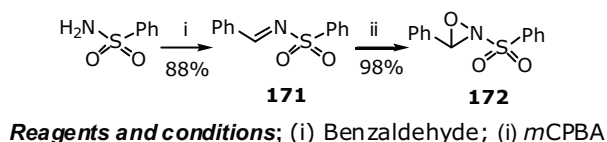
Scheme 4.5.1.5 – Morizaiva's α -hydroxylation of aliphatic esters using Vedejs' reagent.

It is clear from this brief summary that a number of methods are available to accomplish the desired reaction. We considered that the use of oxaziridines as the oxidant in the reaction as it offered an attractive strategy. Oxaziridines have been

shown to react with tetra-substituted enolates; have been successful in the preparation of α -hydroxy esters; and have a proven track record in asymmetric α -hydroxylation reactions - which meets all the criteria for our proposed reaction.

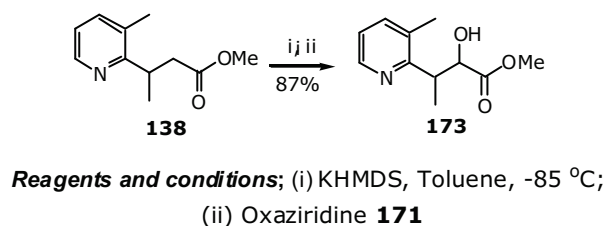
4.5.2 Synthesis of the Oxaziridine

Oxaziridine **172** was prepared from the corresponding sulfonamide by condensation with benzaldehyde and subsequent oxidation with *m*CPBA (**Scheme 4.5.2.1**).



Scheme 4.5.2.1 – Synthesis of oxaziridine **172**.

A test reaction was conducted to evaluate how efficient the oxaziridine was at transferring the oxygen. Ester **138** was subjected to KHMDS to prepare the corresponding enolate, followed by treatment with oxaziridine **172**. The reaction proceeded to give the desired α -hydroxylated product **173** in high yield (**Scheme 4.5.2.2**).

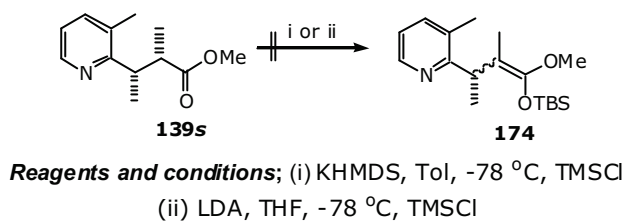


Scheme 4.5.2.2 - α -Hydroxylation of ester **173** using KHMDS and oxaziridine **172**.

Satisfied that the oxaziridine was efficiently transferring the oxygen atom, our studies next focused on identifying enolisation conditions for ester **139s**.

4.5.3 Tetrasubstituted Enolates & Hydroxy Evoninic Acid

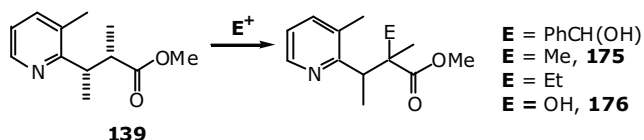
It has been widely documented that silyl ketene acetals are useful substrates in combination with oxaziridines to effect α -hydroxylation. In view of this, initial attempts were made to prepare the silyl ketene acetal of ester **174**. It was hoped that suitable enolisation conditions would be identified allowing us to establish the *E/Z* ratio (**Scheme 4.5.3.1**).



Scheme 4.5.3.1 - Attempted preparation of the silyl ketene acetal of ester **174**.

Unfortunately, both LDA and KHMDS failed to afford the *tetra*-substituted silyl ketene acetal **174** with only ester **139** being recovered in an unchanged *syn:anti* ratio (*dr* 96:4).

Owing to the unsuccessful preparation of the silyl ketene acetal, attention focused on identifying efficient conditions for the enolisation and the subsequent addition to an electrophile (**Table 4.5.3.1**).



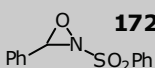
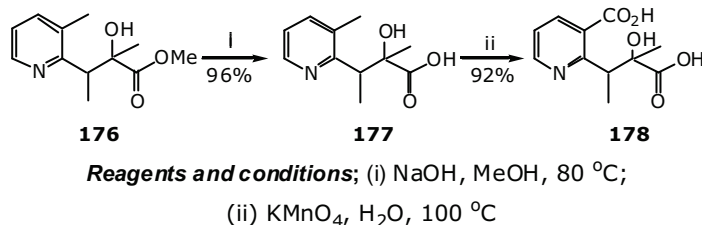
Entry	Base	Electrophile	Solvent	Temp/ °C	Time	Yield/%
1	LDA	PhCHO	THF	-78-25	1h	99
2	LDA	MeI	THF	-78-25	1h	97
3	LDA	MeI	THF	-78-0	1h	----
4	LDA	EtI	THF	-78-0	1h	----
5	KHMDS	MeI	Tol	20	48h	97
6	KHMDS	 172	Tol	20	48h	78 (<i>dr</i> 75:25)

Table 4.5.3.1 - Evaluation of conditions for enolisation and electrophile addition to ester **139**.

Initial attempts to enolise ester **139** using LDA (-78 °C - rt) followed by quenching with benzaldehyde (**Table 4.5.3.1, entry 1**) or MeI (**Table 4.5.3.1, entry 2**) (-78 °C - rt) resulted in the formation of the desired addition products **174** and **175** in 99 and 97% yields, respectively. Attempts to prepare the enolate at a lower temperature (-78 °C - 0 °C) followed by quenching with MeI (**Table 4.5.3.1, entry 3**) or EtI (**Table 4.5.3.1, entry 4**) (-78 °C - rt) gave only recovery of ester **139**. Finally, changing the base from LDA to KHMDS at 25 °C with both MeI and oxaziridine **172** as the electrophile gave good conversion to the desired α -alkylated and α -hydroxylated products **175** and **176**, respectively

in good yields. In the latter reaction the diastereoselectivity was found to be modest [*dr*: 75:25 (**176a**:**176b**)] (**Table 4.5.3.1, entries 5 and 6**).

The mixture of α -hydroxylated esters **176** was subsequently taken forward for the synthesis of the un-natural product hydroxy evoninic acid (**Scheme 4.5.3.2**).



Scheme 4.5.3.2 – Synthesis of (±)-hydroxy evoninic acid **178**.

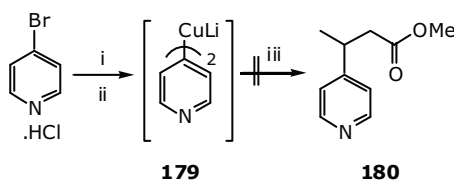
α -Hydroxylated ester **176** was hydrolysed with NaOH in MeOH to give the corresponding monoacid **177** in excellent yield [*dr*: 70:30 (**177a**:**177b**)]. This mixture of acids was subsequently oxidised with KMnO₄ to give hydroxy evoninic acid **178** in excellent yield [*dr*: 70:30 (**178a**:**178b**)]. The assignment of the two diastereoisomers **178a** and **178b** as *syn* or *anti* was not attempted.

4.6 Towards Hydroxy-*iso*-Evoninic Acid via Cuprate 1,4-Addition.

Owing to the successful enantioselective synthesis of (-)-evoninic acid and the synthesis of the un-natural product hydroxy evoninic acid we were now in a position to attempt to transfer the methodology to the C4 position on the pyridine ring and prepare our final target natural product hydroxy-*iso*-evoninic acid.

4.6.1 Unsubstituted 4-Pyridyl Cuprates.

Initial attempts to prepare the 4-pyridyl homocuprate **179** and perform a 1,4-addition to methyl crotonate were promising (**Scheme 4.6.1.1**).⁴⁸

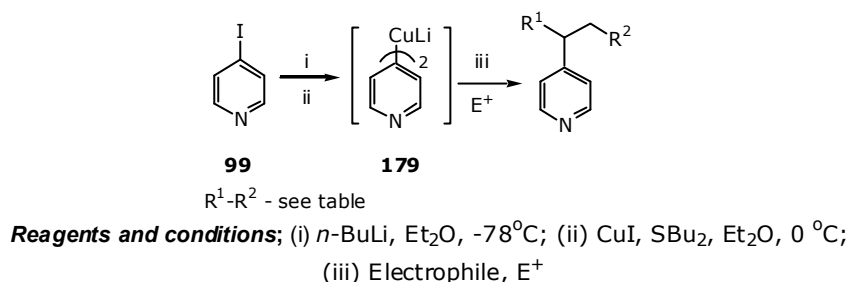


Reagents and conditions; (i) *n*-BuLi, Et₂O, -78 °C; (ii) CuI, SBU₂, Et₂O, 0 °C;
(iii) Methyl crotonate

Scheme 4.6.1.1 – 1,4-Addition of 4-pyridyl cuprate to methyl crotonate.

Analysis of the reaction mixture (HRMS-Cl) confirmed the formation of the desired product **180**. However, we were unable to isolate the desired product due to the very poor conversion.

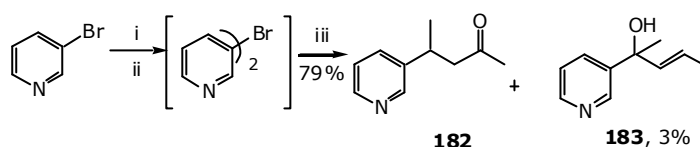
We subsequently decided to revert back to using 4-iodopyridine **99**. The cuprate was formed using the standard conditions and reacted with three Michael acceptors: methyl crotonate, penten-2-one and crotononitrile. These reactions gave the desired products **180**, **166** and **181** in good yields (**Table 4.6.1.1**). This to the best of our knowledge, these are the first 4-pyridyl Gilman cuprates to undergo 1,4-addition reactions.



Entry	Electrophile	Yield/%	Product
1		78	 180
2		86	 166
3		90	 181

Table 4.6.1.1 - 1,4-Addition of the cuprate of 4-iodo pyridine **99** to three Michael acceptors.

Following this, we decided to see whether this methodology was also applicable to a 3-pyridyl cuprate. Gratifyingly, the 1,4-addition of the cuprate derived from 3-bromopyridine to penten-2-one was successful, giving compound **182** in 79% yield (**Scheme 4.6.1.2**).

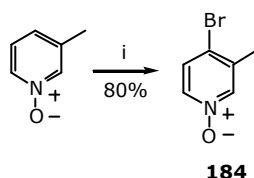


Reagents and conditions; (i) *n*-BuLi, Et₂O, -78°C; (ii) CuI, SBut₂, Et₂O, 0 °C; (iii) penten-2-one

Scheme 4.6.1.2 - 1,4-Addition of the cuprate of 3-bromopyridine to penten-2-one.

4.6.2 Synthesis of 4-Bromo-3-Methyl Pyridine

Next, efforts focused on the preparation of 4-bromo-3-methyl pyridine for the preparation of hydroxy-*iso*-evonic acid. Literature precedent for the preparation of this compound involves bromination of 3-picoline-*N*-oxide using Br₂ and thallium triacetate to give the desired bromide **184** in 82% yield.¹⁷⁵ In our hands this product was obtained in 80% crude yield (**Scheme 4.6.2.1**).

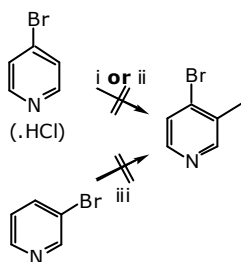


Reagents and conditions; (i) AcOH, Tl(OAc)₃, Br₂.

Scheme 4.6.2.1 – Bromination of 3-picoline-*N*-oxide **184**.

Although the reaction had proceeded well, it was decided that the reaction would be too expensive and hazardous to scale-up given the quantities of thallium triacetate (1 g) required for preparation of just 100 mg of the 3-picoline-*N*-oxide **184**.¹⁷⁵

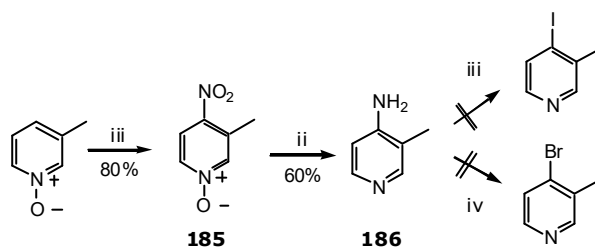
Subsequent attempts to prepare 4-bromo-3-methyl pyridine included: DoM of 4-bromopyridine using LDA, prior to a MeI quench;¹³² DoM of 3-bromopyridine (which has been reported to undergo a halogen dance at -50 °C to the 4-position) using LDA and treatment with MeI;¹⁷⁶ and finally halogen-lithium exchange on the hydrochloride salt of 4-bromopyridine with LDA and transmetallation onto zinc, followed by a MeI quench.¹⁷⁷ However, all three attempts were unsuccessful, only giving trace formation of the desired product (**Scheme 4.6.2.2**).



Reagents and conditions; (i) LDA, MeI, $-78\text{ }^{\circ}\text{C}$; (ii) *n*-BuLi, ZnCl, MeI, $-78\text{ }^{\circ}\text{C}$ - $-40\text{ }^{\circ}\text{C}$
(iii) LDA, MeI, $-50\text{ }^{\circ}\text{C}$;

Scheme 4.6.2.2 – Attempted preparation of 4-bromo-3-methyl pyridine *via* DoM and halogen-lithium exchange.

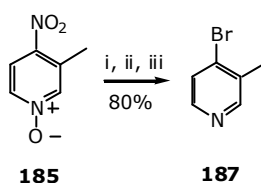
Next we considered using diazotisation reaction conditions. Aminopyridine **186** was prepared by nitration of 3-picoline-*N*-oxide to give nitropyridine **185**, followed by reduction with iron filings in acetic acid to give aminopyridine **186** in reasonable overall yield. Diazotisation of aminopyridine **186** the treatment with both KI¹¹⁵ and CuBr¹⁷⁸ (Sandmeyer conditions) to form the 4-halo-3-methyl pyridine was attempted. To our disappointment, both reactions failed to give any of the desired product (**Scheme 4.6.2.3**).



Reagents and conditions; (i) H₂SO₄, HNO₃, $100\text{ }^{\circ}\text{C}$; (ii) Fe, AcOH, $100\text{ }^{\circ}\text{C}$;
(iii) NaNO₂, KI; (iv) NaNO₂, CuBr

Scheme 4.6.2.3 – Attempts to prepare 4-iodo-3-methyl pyridine *via* diazotisation reactions.

Finally, the elusive 4-bromo-3-methyl pyridine was prepared by treatment of *N*-oxide **185** with PBr_3 in EtOAc at 80 °C to give the desired product according to the method of Abramovitch.¹⁷⁹ The reaction proceeded in high yields, however purification by chromatography was problematic since the product was found to be volatile and distillation from the reaction mixture was inefficient. Changes were therefore made to the work-up procedure utilising differences in the acid-base properties of product **187** and the impurities to give an improved preparation of this compound without the need for further purification by either chromatography or distillation (**Scheme 4.6.2.4**).¹⁷⁹

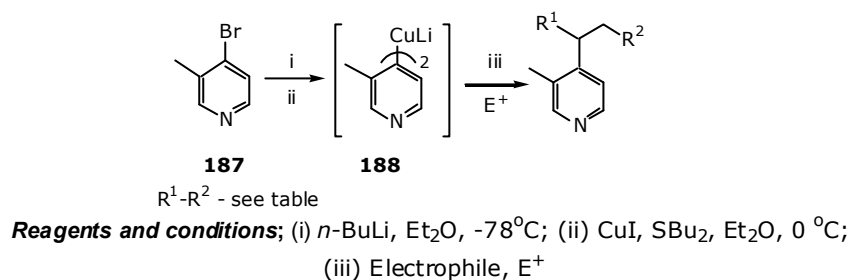


Reagents and conditions: (i) PBr_3 , EtOAc; (ii) NaOH pellets pH ~ 2-3, remove EtOAc layer; (iii) NaOH pellets pH ~ 14, extract into Et_2O .

Scheme 4.6.2.4 – Preparation of 4-bromo-3-methyl pyridine **187** by a modification of the method of Abramovitch .

4.6.3 Synthesis of 4-Pyridyl-3-Methyl Cuprates

4-Bromo-3-methyl pyridine was subjected to the Gilman cuprate reaction conditions. The reaction required higher dilution than the unsubstituted analogue, but to our delight the derived cuprate was successfully added to methyl crotonate, penten-2-one and crotononitrile to furnish the desired products **189**, **190** and **191**, in good yields (**Scheme 4.6.3.1**).



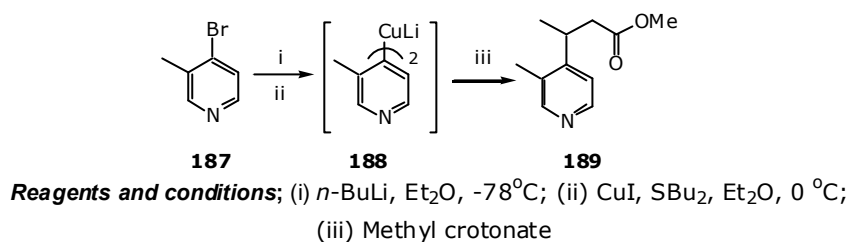
Entry	E ⁺	Yield/%	Product
1		70	
2		82	
3		79	

Table 4.6.3.1 - 1,4-Addition of the cuprate of 4-bromo-3-methyl pyridine **188** to three Michael acceptors.

It is clear from these examples that this reaction is a powerful and versatile tool, for the 1,4-addition of substituted pyridyl systems to a number of unsaturated systems.

4.6.4 Towards the Synthesis of Hydroxy-*iso*-Evoninic Acid

The 1,4-addition of the cuprate of 4-bromo-3-methyl pyridine **187** to methyl crotonate was repeated on large scale to bring material through for the methylation studies (**Table 4.6.4.1**).

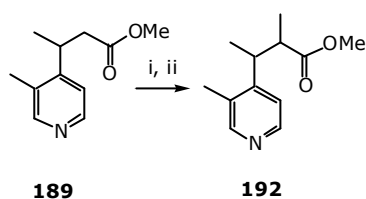


Entry	Amount	Molarity	Yield/%
1	1.00 g	1.0 M	no reaction
2	500 mg	0.1 M	no reaction
3	500 mg	0.01	23
4	210	0.01	71
5	361	0.01	52

Table 4.6.4.1 – Scale up and optimisation of the 1,4-Addition of the cuprate of 4-bromo-3-methyl pyridine **187** to methyl crotonate.

Disappointingly, initial attempts to scale up the reaction to between 500 mg – 1 g failed (**Table 4.6.4.1, entries 1-3**). Reducing the molarity to 0.01 M improved the reaction (**Table 4.6.4.1, entry 3**) giving ester **189** in 23% yield. Finally, conducting the reaction on a smaller scale at 0.01 M gave formation of the desired product in high yield (**Table 4.6.4.1, entry 4**). We were unable to carry out the reaction on larger than 200 mg scale even using the 'optimum' concentration of 0.01 M.

Methylation of ester **189** was attempted next (**Table 4.6.4.2**)



Reagents and conditions; (i) CONDITIONS; (ii) MeI

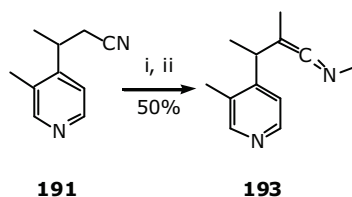
Entry	Conditions	Additive	Outcome
1	KHMDS, Toll, -78 °C, MeI	-----	no reaction
2	KHMDS, Tol, 25 °C, MeI	-----	no reaction
3	KHMDS, Tol, 60 °C, MeI	-----	no reaction
4	LDA, THF, -78 °C, MeI	-----	no reaction
5	LDA, THF, -78 °C, MeI	TMEDA	no reaction
6	LDA, THF, -78 °C, MeI	LiCl	no reaction
7	LDA, THF, -78 °C, MeI	HMPA	no reaction
8	^t BuOK, ^t BuOH, 25 °C, MeI	-----	no reaction
9	NaH, DMF, 25 °C, MeI	-----	see text
10	NaH, <i>d</i> ₆ -DMSO, 25 °C, MeI	-----	no reaction
11	NaNH ₂ , NH ₃ , -78 °C, MeI	-----	no reaction
12	^t Bu ₄ NI, KOH, MeCN, MeI	-----	no reaction
13	^t Bu ₄ NBr, KOH, CH ₂ Cl ₂ , MeI	-----	no reaction

Table 4.6.4.2 – Attempted alkylation of ester **189**.

Methylation of ester **189** was attempted using the conditions that were successful for the methylation in the diastereoselective synthesis of evoninic acid, i.e. KHMDS, MeI, toluene at -78 °C for 24 h. Disappointingly, none of the desired product was observed using these conditions (**Table 4.6.4.2, entry 1**). Use of KHMDS at both 25 and 60 °C gave none of the desired product (**Table 4.6.4.2, entries 2 & 3**). Using LDA at -78 °C with or without TMEDA, LiCl and HMPA did not resolve the situation, with no evidence of the desired product in any of the reactions (**Table 4.6.4.2, entries 4–7**). It was apparent from these results that this substrate is not reactive towards traditional methylation conditions. Of note also was the broadness of the aromatic signals of the starting material in ¹H NMR (CDCl₃). We concluded that these two observations could be related and so decided to take a ¹H NMR of the starting material in *d*₆-DMSO. Surprisingly, the aromatic peaks now appeared to be completely resolved; which suggested that the starting material was aggregating in less polar solvents. We considered that this could explain the problems that were being encountered with the enolisation

of the substrate in toluene or THF. Consequently, we investigated the use of more polar solvents, with the view to break up the aggregates. First we attempted to use t BuOK in t BuOH at 25 °C. The reaction turned red in colour on addition of the ester to the base (which was assumed to indicate enolate formation), but unfortunately again the reaction failed to proceed, with only starting material recovered (**Table 4.6.4.2, entry 8**). Next we attempted to use NaH as the base in DMF (**Table 4.6.4.2, entry 9**). This too gave a distinctive red colour on addition of the ester **189** to the base. For the first time trace quantities of the desired product **192** were observed by MS-CI analysis, however ^1H NMR analysis showed many pyridyl containing products. The reaction was scaled-up in an attempt to isolate a sample of the desired product. Unfortunately, removal of the DMF proved problematic, involving laborious multiple washes with water and flash chromatography leading to an extremely low yield of the reaction mixture containing only trace quantities of the required product. Next we attempted to conduct the reaction in d_6 -DMSO to see if the product could be observed directly by ^1H NMR (**Table 4.6.4.2, entry 10**). However, although this reaction also turned the distinctive red colour, none of the desired product was observed, even by MS-CI analysis. The reaction was next attempted using sodiamide in liquid ammonia (**Table 4.6.4.2, entry 11**). Once again the reaction failed to produce the anticipated product, but instead a mixture of unidentifiable products. Finally, phase transfer methylation was evaluated. In two parallel reactions, ester **189** was exposed to two sets of solid-liquid phase transfer conditions: a suspension of crushed KOH and $t\text{Bu}_4\text{NI}$ in MeCN, and a suspension of crushed KOH and $t\text{Bu}_4\text{Br}$ in CH_2Cl_2 , followed by the addition of MeI. In both cases the conditions failed to provide the required alkylated product (**Table 4.6.4.2, entries 12 & 13**). It was concluded that methylation of this ester substrate was being severely hampered by an unusual aggregation phenomenon specific to this substrate ester **189** and so this approach was reluctantly abandoned.

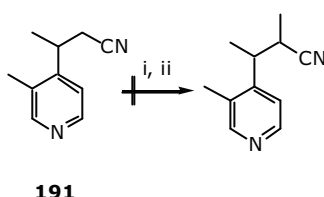
It was decided to explore the α -methylation of nitrile **191** for the synthesis of hydroxy-*iso*-evoninic acid **3**. One reason for doing this was that this nitrile displayed none of the aforementioned signal broadening in the ^1H NMR observed with the corresponding ester. Methylation using KHMDS, in toluene at -78 °C with MeI gave interesting results. Alkylation was observed to occur at the required position, but, unfortunately, methylation of the nitrile was also observed, affording iminoketene **193** (**Scheme 4.6.4.1**).



Reagents and conditions; (i) KHMDS, Tol, -78 °C, 24 h; (ii) MeI

Scheme 4.6.4.1 - Attempted α -methylation of nitrile **191** with excess MeI.

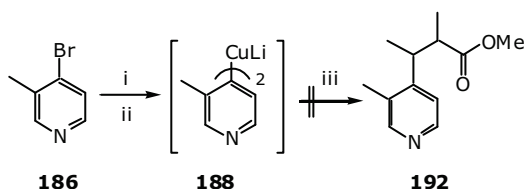
The reaction was then repeated, taking care not to add an excess of MeI. Disappointingly, no reaction took place - it appeared that we were unable to repeat the alkylation either at the required position or on the nitrile (**Scheme 4.6.4.2**).



Reagents and conditions; (i) KHMDS, Tol, -78 °C, 24 h;
(ii) 0.99eq MeI

Scheme 4.6.4.2 - Attempted α -methylation of nitrile **191** with 1 eq. of MeI.

Finally, despite the poor yields obtained in the 1,4-addition of the cuprate of 2-bromo-3-methyl pyridine to α,β -substituted- α,β -unsaturated esters we decided to see if we could obtain an authentic sample of the desired product by the 1,4-addition of the cuprate of 4-bromo-3-methyl pyridine to methyl tiglate (**Scheme 4.6.4.3**).



Reagents and conditions; (i) *n*-BuLi, Et₂O, -78 °C; (ii) CuI, SBU₂, Et₂O, 0 °C;
(iii) Methyl tiglate

Scheme 4.6.4.3 - Attempted 1,4-addition of the cuprate of 4-bromo-3-methyl pyridine **186** to methyl tiglate.

To our disappointment, the reaction was unsuccessful, with none of the desired 1,4-addition product detected.

It appears from these studies that the installation of the methyl group β to the pyridyl ring is not as trivial as we had hoped. It was initially envisaged that the synthesis of hydroxy-*iso*-evoninic acid could be achieved *via* the same route as that developed for both the enantioselective synthesis of (-)-evoninic acid and the

synthesis of the un-natural product hydroxy evoninic acid. However, it is apparent that the 3,4-disubstituted pyridyl unit presents some additional challenges. The difference in reactivity can probably be attributed to the difference in the nucleophilicities of the pyridine nitrogen lone pair in the iso-evoninic acid series as compared to the evoninic acid series; the C2 substituent in the latter series sterically shields the lone pair rendering it minimally nucleophilic whereas in the *iso*-evoninic acid series the relatively unhindered pyridine nitrogen is significantly nucleophilic. Clearly a new approach for the construction of hydroxy-*iso*-evoninic acid is required: Some possibilities for this are discussed in the next section.

5 Conclusions & Future Work

5.1 Conclusions

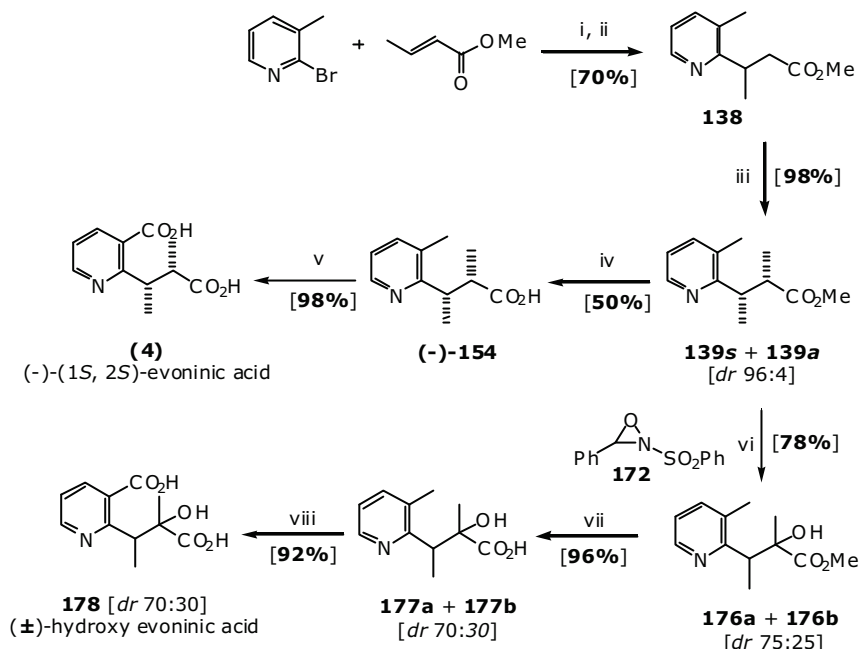
5.1.1 Rhodium Catalysed 1,4-Addition Work

We have determined that 4-pyridyl boronic acid derivatives are unsuitable substrates for rhodium catalysed 1,4-addition reactions. This is primarily due to the instability of these substrates to the aqueous reaction conditions. We have also established that 4-pyridyl trialkylstannane substrates are too un-reactive to undergo rhodium catalysed 1,4-addition reactions although these substrates are more resistant to destannylation than their analogous 4-pyridyl boronic acids and esters are to deboronation. The lack of reactivity was initially postulated to be as the result of the highly electron deficient nature of the pyridyl ring. However, attempts to make the C4-position of the 4-pyridyl stannanes more nucleophilic by the incorporation of electron donating functionality at the C3-position (e.g. OMe and OCONe₂) did not improve the situation. These findings and also the fact that electron deficient aryl stannanes such as *p*-FC₆H₄SnMe₃ have successfully been used by others to undergo rhodium catalysed 1,4-additions led us to consider that the nucleophilic pyridyl might be acting as a ligand on rhodium and preventing catalysis. To circumvent this problem a series of *N*-oxide and methyl pyridinium salts of 4-pyridyl stannanes were screened for 1,4-addition. Using the 4-pyridyl trimethyl stannane-*N*-methyl tosylate pyridinium salt in a stoichiometric rhodium catalysed 1,4-addition reaction to methyl crotonate gave for the first time evidence of the 1,4-addition product by CI-MS analysis. To our disappointment, we were unable to optimise the conditions this transformation for it to be synthetically useful. In view of the time already invested on this methodology, and the lack of success, this strategy was subsequently abandoned as a feasible route to our target molecule.

5.1.2 Cuprate Mediated 1,4-Addition Work

We have investigated the feasibility of using pyridyl cuprate reagents to conduct 1,4-addition reactions. The 1,4-addition of 3-methyl-2-pyridyl cuprates to enones, enoates and unsaturated nitriles have been shown for the first time to be synthetically useful, obtaining the 1,4-addition products in good yields. This methodology has enabled an expedient, highly diastereo- and enantioselective synthesis of (-)-evoninic acid, using a lipase mediated hydrolytic kinetic resolution step (ester **139s** → acid **154**) to control the absolute stereochemistry. Ester

139s was also used as a model for the synthesis of hydroxy-*iso*-evoninic acid. Thus un-natural product, hydroxy evoninic acid, was prepared *via* α -hydroxylation of ester **139s** using an oxaziridine **172** and saponification of the ester to give the acid **177** (Scheme 5.1.2.1).



Reagents and conditions: (i) *n*-BuLi, Et₂O, -78 °C; (ii) CuI, SBU₂, 0 °C; (iii) KHMDS, MeI, Tol, -78 °C; (iv) Lipase P. Fluorecens, potassium phosphate pH 7.0 buffer, 37 °C; (v) KMnO₄, H₂O, 100 °C; (vi) KHMDS, Oxaziridine **172**, 25 °C; (vii) NaOH, MeOH, 60 °C; (viii) KMnO₄, H₂O, 100 °C

Scheme 5.1.2.1– Synthesis of (-)-evoninic acid (**4**) and hydroxy evoninic acid **178**.

The copper catalysed 1,4-addition of Grignard reagents using a CuBr.SMe₂ – JOSIPHOS™ system, first developed by Feringa for alkyl magnesium bromides, has been shown for the first time to be synthetically useful for the addition of pyridyl Grignard reagents. Through 'in-situ' protection of the pyridine nitrogen we found that the 1,4-addition of both 2- and 4-pyridyl Grignard reagent to penten-2-one occurs in excellent yield, with exclusive formation of the 1,4-addition product at low temperature (-75 °C) for the 2-pyridyl Grignard.

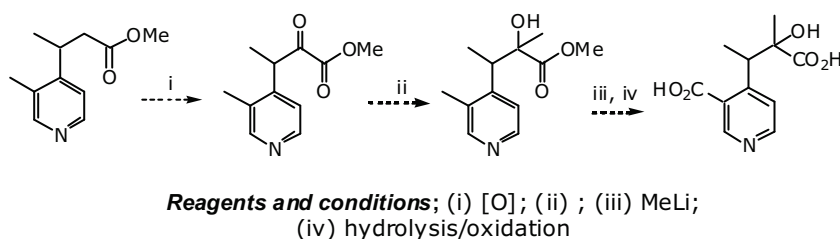
Finally, attempts were made to prepared hydroxy-*iso*-evoninic acid. This required the development of a 1,4-addition reaction for 4-pyridyl cuprates. Both 4-pyridyl and 3-substituted-4-pyridyl cuprate reagents were found to participate in 1,4-addition reactions to an enone, an enoate and an unsaturated nitrile giving the 1,4-addition products in good yields. These, to the best of our knowledge, are the first 4-pyridyl cuprates to participate in 1,4-addition reactions.

The synthesis of hydroxy *iso*-evoninic acid using a strategy analogous to that used for the synthesis of hydroxy evoninic acid but starting from the product of 3-methyl-4-pyridyl cuprate 1,4-addition to methyl crotonate (i.e. **189**) was also investigated. Unfortunately, installation of the methyl group α to the ester on this substrate through a variety of methods proved to be impossible. Some potential methods to complete the synthesis are presented next.

5.2 Future Work

5.2.1 Synthesis of Hydroxy-*iso*-Evoninic Acid

We envisage two strategies to complete the synthesis of hydroxy-*iso*-evoninic acid. First, since it appears that it is not possible to generate the enolate of methyl ester **189** and effect methylation an alternative strategy would be to oxidise the α -position under acidic conditions. This would allow access to the α -keto ester, methylation of which would give hydroxy-*iso*-evoninic acid (**Scheme 5.2.1.1**).

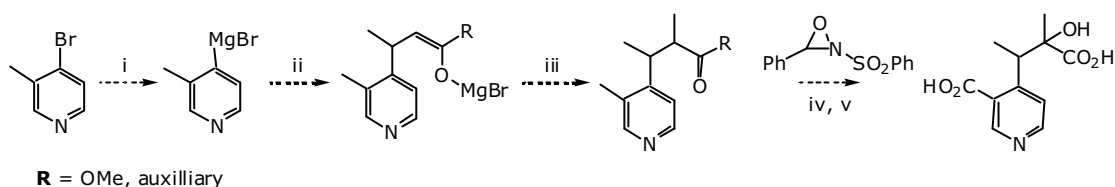


Scheme 5.2.1.1 – Proposed synthesis of hydroxy-*iso*-evoninic acid *via* an α -keto ester intermediate.

Second, the copper catalysed 1,4-addition methodology developed for pyridyl reagents during the course of our studies could be exploited. The key advantage of this method over the lithium cuprate approach is that it should be possible to trap out the magnesium enolate generated in the 1,4-addition process using MeI and so generated the desired dimethyl product **192** without recourse to the problematic re-enolisation step. To this end, we are confident, that exclusive 1,4-addition of the 4-pyridyl Grignard reagent to penten-2-one is possible by reducing the temperature of the reaction to $-75\text{ }^{\circ}\text{C}$ (as shown for the 2-pyridyl analogue).

With regards to use of α,β -unsaturated esters; very recently, Feringa has reported the first copper catalysed enantioselective 1,4-addition of alkyl Grignard reagents to α,β -unsaturated esters.⁸⁷ He reports the preparation of an air-stable copper complex, prepared from copper bromide dimethyl sulfide complex and a JosiPhosTM ligand prior to the 1,4-addition reaction. It is possible that by either

using this pre-formed $\text{CuBr} \cdot \text{SMe}_2$ -JOSIPHOSTM catalyst with methyl crotonate or by using a chiral auxiliary approach with an excess of $\text{CuBr} \cdot \text{SMe}_2$, an asymmetric 1,4-addition of pyridyl Grignard reagents will be possible. It should then be possible to trap the magnesium enolate with MeI to effect the installation of the problematic methyl group in the α -position as required for our synthesis of hydroxy-*iso*-evoninic acid (**Scheme 5.2.1.2**).



Reagents and conditions; (i) Mg turnings, Et_2O ; (ii) 110 mol% $\text{CuBr} \cdot \text{SMe}_2$, chiral acyl sulfonamide, $t\text{BuOMe}$, -78°C **or** $\text{CuBr} \cdot \text{SMe}_2$ -JOSIPHOSTM catalyst, methyl crotonate, $t\text{BuOMe}$, -78°C ; (iii) MeI quench; (iv) KHMDS, oxaziridine, Tol, 25°C ; (v) hydrolysis/oxidation

Scheme 5.2.1.2 – Proposed synthesis of hydroxy-*iso*-evoninic acid using a copper catalysed 1,4-addition reaction.

5.2.2 Synthesis of Hypoglaunine B and Emarginatine F

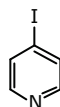
Finally, an efficient coupling of the correct stereoisomer of hydroxy *iso*-evoninic acid **3** and (-)-evoninic acid with an appropriate euonyminol derivative is required for the first synthesis of hypoglaunine B (**1**) and emarginatine F (**8**). The only literature precedent for this coupling process is Yamada's resynthesis of evonine (**6**) from evoninol and dimethyl evoninate.²¹ The synthesis of natural (-)-euonyminol is in progress in our lab and it is expected that material from these efforts will be employed for these studies.

6 Experimental

General Directions:

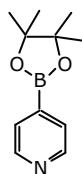
All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in flame-dried glassware. Yields refer to chromatographically and spectroscopically (^1H -NMR) homogenous materials, unless otherwise indicated.

Solvents and reagents: See appendices 1 & 2. **Chromatography:** Flash chromatography (FC) was performed on silica gel (Merck Kieselgel 60 F₂₅₄ 230-400 mesh) according to the method of W.C. Still,¹⁸⁰ unless otherwise indicated. Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed plates pre-coated with silica (0.2 mm, 60 F₂₅₄) which were visualized either by quenching of ultraviolet fluorescence (λ_{max} = 254 and 366 nm) or by charring with 10% KMnO₄ in 1M H₂SO₄. **Melting points:** were determined on a Kofler hot stage. **Infra red spectra:** were recorded as KBr discs on Perkin-Elmer Paragon 1000 fourier transform spectrometer. Only selected absorbances (λ_{max}) are reported. **^1H NMR spectra:** were recorded at either 270, 400 or 500 MHz on Jeol 270 GSX, Bruker AMX-400 or Bruker DRX-500 instruments respectively. Chemical shifts (δ_{H}) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. Coupling constants (J) are reported to the nearest 0.5 Hz. **^{13}C NMR spectra:** were recorded at either 67.5, 100 or 125 MHz on Jeol 270 GSX, Bruker AMX-400 or Bruker DRX-500 instruments respectively. Chemical shifts (δ_{C}) are quoted in ppm, referenced to the appropriate residual solvent peak. Degenerate peaks are suffixed by the number of carbons. **Mass spectra:** Low resolution mass spectra (m/z) were recorded on either a VG platform II or VG AutoSpec spectrometers, with only molecular ions (M^+ , MH^+ , MNH_4^+) and major peaks being reported with intensities quoted as percentages of the base peak. High Resolution Mass Spectrometry (HRMS) measurements are valid to ± 5 ppm. CSP-HPLC was performed on a Hewlett Packard series 1100 instrument using Diacel Chiralcel OD (0.46 cm $\times$ 25.0 cm) column. CD spectra were recorded between 280-380 nm in CHCl₃/H₂O (1 mg 5 mL) with a Jasco J600 spectropolarometry using 10 min quartz cuvettes at 20 °C.

4-Iodopyridine (99).¹¹⁵

C₅H₄IN
 Exact Mass: 204.94
 Mol. Wt.: 205.00
 C, 29.29; H, 1.97; I, 61.91; N, 6.83

To a cooled (−10 °C) solution of *4-aminopyridine* (2.00 g, 21.0 mmol) in 48% aqueous tetrafluoroboric acid (17 mL) was added portion-wise sodium nitrite (1.58 g, 23.0 mmol) ensuring that no gas evolution could be detected. The resultant slurry was stirred at −10 °C for 30 min. The reaction mixture was filtered to afford a white solid (CAUTION! diazonium salt, potentially explosive – keep damp). The solid was quickly transferred portion-wise to a stirring saturated solution of potassium iodide (5.60 g, 33 mL) acetone/H₂O (40:60). The resultant brown slurry was decolourised with saturated sodium thiosulphate (10 mL) and carefully neutralised with sodium carbonate (20 mL) and then extracted into Et₂O (3 × 50 mL). The organic extracts were combined and washed with H₂O (3 × 100 mL) and brine (100 mL) and dried over MgSO₄ and concentrated *in vacuo* to give a yellow solid. Purification by FC (CHCl₃/Et₂O, 75:25) afforded *iodopyridine 99* (3.01 g, 70%) as pale yellow needles. mp 100–102 °C (Et₂O) [Lit., ¹¹⁵ mp 100 °C (Et₂O)]; R_f 0.43 (CHCl₃:Et₂O, 75:25); δ_H (CDCl₃, 300 MHz) 7.68 (2H, d, *J* 5.0 Hz, CCH) and 8.27 (2H, d, *J* 5.0 Hz, NCH). MS (CI⁺) *m/z* 206 (MH⁺, 100), 223 (MNH₄⁺, 10), 116 (5), 112 (10), 102 (10), 80 (10); HRMS (CI⁺) calcd for C₅H₅IN (MH⁺) 205.9467, found 205.9462 (? = − 2.5 ppm). [Lit., ¹¹⁵ ¹H-NMR (250 MHz, CDCl₃) δ = 7.68 (d, 2H, ³J_{H-H} = 6 Hz), 8.26 (d, 2H, ³J_{H-H} = 6 Hz)].

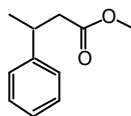
2-(4-Pyridyl)-4,4,5,5,-tetramethyl-1,3-dioxaborolane (100).¹¹⁵

C₁₁H₁₆BNO₂
 Exact Mass: 205.13
 Mol. Wt.: 205.06
 C, 64.43; H, 7.86; B, 5.27; N, 6.83; O, 15.60

To a slurry of *4-iodopyridine 99* (500 mg, 2.1 mmol) in Et₂O (30 mL) at −78 °C was added a solution of *n*-BuLi (2.5 M in hexanes, 1.2 mL, 2.9 mmol). The reaction mixture was left to stir for 20 min, after which tri-*n*-butylborate (800 μL, 2.9 mmol) was added dropwise. The reaction mixture was slowly warmed to room temperature over a period of 2 h, then, pinacol (461 mg, 3.9 mmol) was added in one portion. After 10 min the reaction was quenched with acetic acid (144 mg,

2.4 mmol). The resultant pale yellow slurry was filtered through a plug of celite®. The filtrate was concentrated *in vacuo* to give a pale yellow oil. Purification by trituration (MeCN) afforded *pinacol ester 100* (100 mg, 21%) as a white microcrystalline powder. mp 151-152 °C (cyclohexane) [Lit.,¹¹⁵ 151 °C (cyclohexane)]; R_f 0.03 (nHexane/EtOAc, 90:10); δ_H (CDCl₃, 300 MHz) 1.38 (12H, s, CH₃), 7.64 (2H, d, *J* 4.0 Hz, CCH) and 8.65 (2H, d, *J* 4.0 Hz, NCH). [Lit.,¹¹⁵ ¹H-NMR (250 MHz, CDCl₃) δ = 1.34 (s, 12H), 7.61 (d, ³J_{H-H} = 5.7 Hz), 8.62 (d, 2H, ³J_{H-H} = 5.7 Hz)].

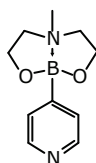
3-Phenylbutyric acid methyl ester (102).⁹¹



C₁₁H₁₄O₂
 Exact Mass: 178.10
 Mol. Wt.: 178.23
 C, 74.13; H, 7.92; O, 17.95

Rh(acac)(C₂H₄)₂ (6 mg, 0.02 mmol), BINAP (23 mg, 0.04 mmol) and *phenyl boronic acid* (200 mg, 1.60 mmol) were dissolved in dioxane (12 mL) and H₂O (2 mL). The reaction mixture was stirred for 30 minutes, after which time the methyl crotonate (82 mg, 0.80 mmol) was added. The reaction mixture was stirred at 100 °C for 2 h. The product was extracted into benzene (50 mL), washed with H₂O (3 × 50 mL), brine (50 mL) and dried over MgSO₄ and concentrated *in vacuo* to give needle-like crystals. Purification by FC (EtOAc) afforded *ester 102* (217 mg, 78%) as a pale yellow oil. R_f 0.58 (EtOAc); δ_H (CDCl₃, 300 MHz) 1.28 (3H, d, *J* 7.0 Hz, CH₃), 2.51-2.66 (2H, m, CH₂), 3.25-3.33 (1H, m, CHCH₃), 3.63 (3H, s, OCH₃) and 7.18-7.33 (5H, m, Ar-H). [Lit.,⁹¹ ¹H-NMR (CDCl₃): δ 7.31-7.27 (m, 2H), 7.24-7.18 (m, 3H), 3.62 (s, 3H), 3.31-3.24 (m, 1H), 2.62 (dd, ²J_{HH} = 15.1 Hz and ³J_{HH} = 7.0 Hz, 1H), 2.54 (dd, ²J_{HH} = 15.1 Hz and ³J_{HH} = 8.2 Hz, 1H), 1.30 (d, ³J_{HH} = 7.0 Hz, 3H).]

4-*N*-Methyldiethanolamine pyridyl borate (103).¹¹⁶

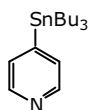


C₁₀H₁₅BN₂O₂
 Exact Mass: 206.12
 Mol. Wt.: 206.05
 C, 58.29; H, 7.34; B, 5.25; N, 13.60; O, 15.53

To a solution of *iodopyridine 99* (500 mg, 2.6 mmol) in Et₂O (6 mL) at -78 °C was added a solution of *n*-BuLi (2.42 M in hexanes, 1.4 mL, 1.3 mmol). The

reaction mixture was left to stir for 1 h, after which time the tri-*n*-butylborate (746 mg, 3.2 mmol) was added dropwise. The reaction mixture was warmed to 25 °C over a period of 2 h, after which *N*-methyldiethanolamine (900 µL, 3.2 mmol) was added dropwise and the reaction mixture left to stir for a further 30 min. The reaction mixture was quenched with acetic acid (156 mg, 2.6 mmol) and filtered through a plug of celite®. The filtrate was concentrated *in vacuo* to afford *pyridyl borate* **103** (135 mg, 25%) as a yellow oil. *R*_f 0.02 (CHCl₃/Et₂O, 75:25); δ_H (CDCl₃, 270 MHz) 2.01 (3H, s, NCH₃), 3.00-3.07 (2H, m, *equatorial* CH₃NCH), 3.21-3.25 (2H, m, *axial* CH₃NCH), 4.09-4.28 (4H, m, OCH₂), 7.58 (2H, dd, *J* 6.0 and 1.5 Hz, CCH) and 8.50 (2H, dd, *J* 6.0 and 1.5 Hz, NCH).¹¹⁵

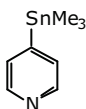
4-Pyridyl tri-*n*-butylstannane (**105**).¹¹⁹



C₁₇H₃₁NSn
 Exact Mass: 369.15
 Mol. Wt.: 368.14
 C, 55.46; H, 8.49; N, 3.80; Sn, 32.25

Snieckus' method of preparation of 4-pyridyl tri-*n*-butylstannane¹¹⁹ was modified as follows: PhLi was substituted for *n*-BuLi and 4-bromopyridine was substituted for 4-iodopyridine.

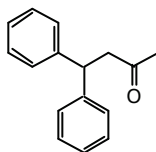
To a stirring solution of 4-iodopyridine **99** (1.00 g, 5.2 mmol) in Et₂O (15 mL) at -78 °C was added a solution of *n*-BuLi (2.4 M in hexanes, 26 µL, 6.2 mmol). The reaction mixture was left to stir for 1 h, after which time the tri-*n*-butylstannane chloride (184 µL, 6.8 mmol) was added dropwise. The reaction mixture was slowly warmed to room temperature over a period of 2 h, after which it was quenched with H₂O (20 mL) and extracted into chloroform (3 × 50 mL). The organic extracts were combined, washed with H₂O (3 × 50 mL) and brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to give a yellow oil. Purification by reverse phase C18 FC (CH₃CN/CHCl₃, 90:10 → CH₃CN/CHCl₃, 60:40) afforded *stannane* **105** (520 mg, 87%) as a pale yellow oil. *R*_f 0.65 (CHCl₃/Et₂O, 75:25); δ_H (CDCl₃, 300 MHz) 0.92 (9H, q, *J* 7.0 Hz, CH₃), 1.12 (6H, t, *J* 8.0 Hz, SnCH₂), 1.19-1.43 (6H, m, CH₃CH₂), 1.52-1.70 (6H, m, CH₂), 7.42 (2H, d, *J* 5.0 Hz, CCH) and 8.50 (2H, d, *J* 5.0 Hz, NCH). MS (CI⁺) *m/z* 370 (MH⁺, 100), 368 (80), 366 (50), 80 (10); HRMS (CI⁺) calcd for C₁₇H₃₁N¹²⁰Sn (MH⁺) 370.1556 found 370.1547 (? = - 0.9 ppm).

4-Pyridyl trimethylstannane (106).¹²⁶

C₈H₁₃NSn
 Exact Mass: 243.01
 Mol. Wt.: 241.91
 C, 39.72; H, 5.42; N, 5.79; Sn, 49.07

Phillips' method of preparation of 4-pyridyl trimethylstannane¹²⁶ was modified as follows: 4-bromopyridine was substituted for 4-iodopyridine.

To a solution of *4-iodopyridine* **99** (1.00 g, 5.2 mmol) in Et₂O (30 mL) at -78 °C was added a solution of *n*-BuLi (2.4 M in hexanes, 2.6 mL, 6.2 mmol). The reaction mixture was left to stir for 1 h, after which the trimethylstannane chloride (6.8 mL, 6.8 mmol) was added dropwise. The reaction mixture was warmed to room temperature over a period of 2 h, after which it was quenched with H₂O (20 mL) and extracted into CHCl₃ (3 × 50 mL). The organic extracts were combined and washed with H₂O (3 × 50 mL) and brine (50 mL), then dried over MgSO₄ and concentrated *in vacuo* to give a yellow oil. Purification by reverse phase C18 FC (CH₃CN/CHCl₃, 75:25) afforded *stannane* **106** (1.0 g, 80%) as a pale yellow oil. *R*_f 0.40 (CHCl₃:Et₂O, 75:25); Bp: 240-241 °C/0.5 mmHg (Kugelrohr) [Lit.,¹²⁶ 240 °C]; δ_H (CDCl₃, 500 MHz) 0.39 [9H, (83% ^{116,118,120,122,124}Sn), s; (17% ^{117,119}Sn), t, *J* 35.0 Hz, SnCH₃], 7.39 (2H, d, *J* 7.0 Hz, NCHCH) and 8.50 (2H, d, *J* 7.0 Hz, NCH); MS (CI⁺) *m/z* 243 (MH⁺, 100), 241 (80), 239 (50), 90 (10); HRMS (CI⁺) calcd for C₈H₁₃N¹¹⁸Sn (MH⁺) 241.0779, found 241.0779 (? = 0.0 ppm).

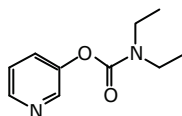
4,4-Diphenylbutan-2-one (107).⁹⁷

C₁₆H₁₆O
 Exact Mass: 224.12
 Mol. Wt.: 224.30
 C, 85.68; H, 7.19; O, 7.13

To a solution of [Rh(cod)(MeCN)₂]BF₄ (7 mg, 0.02 mmol) and *4-phenylbut-3-en-2-one* (146 mg, 1.00 mmol) in THF (1 mL) was added trimethylphenylstannane (289 mg, 1.20 mmol) and H₂O (20 μL) and the resultant reaction mixture heated to reflux for 2 h. The reaction mixture was cooled to 25 °C and extracted into Et₂O (20 mL). The organics were combined and washed with H₂O (3 × 20 mL), brine (100 mL), dried over MgSO₄ and concentrated *in vacuo* to give a yellow oil.

Purification by FC (hexane/EtOAc, 90:10), afforded *ketone* **107** (224 mg, 70%) as a white amorphous powder. R_f 0.10 (hexane/EtOAc, 90:10); δ_H ($CDCl_3$, 300 MHz) 2.10 (3H, s, CH_3), 3.21 (2H, d, J 7.5 Hz, CH_2), 4.62 (1H, t, J 7.5 Hz, CH) and 7.18-7.33 (10H, Ar-H). MS (CI^+) m/z 242 (MNH_4^+ , 100), 226 (10), 206 (10), 167 (30); HRMS (CI^+) calcd for $C_{16}H_{20}NO$ (MNH_4^+) 242.1545, found 242.1534 (? = - 1.1 ppm).

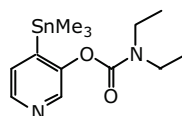
3-Pyridyl diethylcarbamate (**109**).¹²⁸



$C_{10}H_{14}N_2O_2$
Exact Mass: 194.11
Mol. Wt.: 194.23
C, 61.84; H, 7.27; N, 14.42; O, 16.47

To a solution of *3-hydroxypyridine* (2.00 g, 2.1 mmol) in benzene was added triethylamine (3.6 mL, 2.5 mmol) and diethyl carbamyl chloride (3.2 mL, 2.5 mmol) and the resultant reaction mixture heated to reflux for 24 h. The reaction mixture was cooled to 25 °C and concentrated *in vacuo*. The resultant brown oil was diluted with $CHCl_3$ (100 mL) and washed with H_2O (3 $\times$ 100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford *carbamate* **109** (4.07 g, 99%) as a golden oil. R_f 0.08 ($CHCl_3/Et_2O$, 75:25); δ_H ($CDCl_3$, 300 MHz) 1.15 (3H, t, J 7.5 Hz, CH_3CH_2), 1.19 (3H, t, J 7.5 Hz, CH_3CH_2), 3.31 (2H, q, J 7.5 Hz, CH_3CH_2), 3.35 (2H, q, J 7.5 Hz, CH_3CH_2), 7.44 (1H, dd, J 5.0 and 8.0 Hz, CHCHCH), 7.45 (1H, ddd, J 2.0, 4.0 and 8.0 Hz, CHCHCO), 8.13 (1H, d, J 4.0, NCHCO) and 8.37 (1H, d, J 2.0 Hz, NCHCH). MS (CI^+) m/z 195 (MH^+ , 100), 127 (10), 100 (40); HRMS (CI^+) calcd for $C_{10}H_{15}N_2O_2$ (MH^+) 195.1134, found 195.1130 (? = - 1.9 ppm).

3-Pyridyl diethylcarbamyl-4-trimethylstannane (**110**).^{129,130}

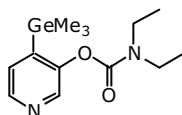


$C_{13}H_{22}N_2O_2Sn$
Exact Mass: 358.07
Mol. Wt.: 357.04
C, 43.73; H, 6.21; N, 7.85; O, 8.96; Sn, 33.25

To a solution of freshly distilled TMEDA (1.6 mL, 10.8 mmol) in THF (20 mL) at - 78 °C was added a solution of *sec*-BuLi (1.3 M in hexanes, 8.3 mL, 10.8 mmol) dropwise. The resultant bright yellow solution was left to stir for 1 h, after which time a solution of *carbamate* **109** (1.00 g, 5.1 mmol) in THF (5 mL) was added dropwise. The resultant red solution was left to stir for a further 1 h.

Trimethylstannane chloride (1.01 g, 5.1 mmol) was added dropwise to the stirring solution. The reaction mixture was warmed to 25 °C over a period of 2 h, after which it was concentrated *in vacuo* to give a red, viscous oil. Purification by FC (CHCl₃/Et₂O, 50:50) afforded *stannane* **110** (1.07 g, 60%) as a pale yellow oil. *R*_f 0.43 (CHCl₃/Et₂O, 50:50); ν_{max} /cm⁻¹ (Neat) 1723 (C=O), 1639, 1396 and 1267; δ_{H} (CDCl₃, 400 MHz) 0.32 [9H, (83% ^{116,118,120,122,124}Sn), s; (17% ^{117,119}Sn), t, *J* 27.5, SnCH₃], 1.21 (3H, t, *J* 7.0 Hz, CH₃CH₂), 1.25 (3H, t, *J* 7.0 Hz, CH₃CH₂), 3.40 (2H, q, *J* 7.0 Hz, CH₃CH₂), 3.44 (2H, q, *J* 7.0 Hz, CH₃CH₂), 7.37 (1H, d, *J* 4.5 Hz, CHCHCH), 8.32 (1H, s, NCHCO) and 8.35 (1H, d, *J* 4.5 Hz, NCHCH); δ_{C} (CDCl₃, 100 MHz) -9.1 (3q), 13.2 (q), 14.2 (q), 41.7 (t), 42.1 (t), 130.8 (d), 143.1 (d), 144.9 (s), 145.2 (d), 153.5 (s) and 154.0 (s). MS (CI⁺) *m/z* 359 (MH⁺, 100), 357 (80), 355 (50), 100 (10); HRMS (CI⁺) calcd for C₁₃H₂₃N₂O₂¹²⁰Sn (MH⁺) 359.0782, found 359.0788 (? = + 0.6 ppm).

3-Pyridyldiethylcarbamyl-4-trimethylgermane (**111**).

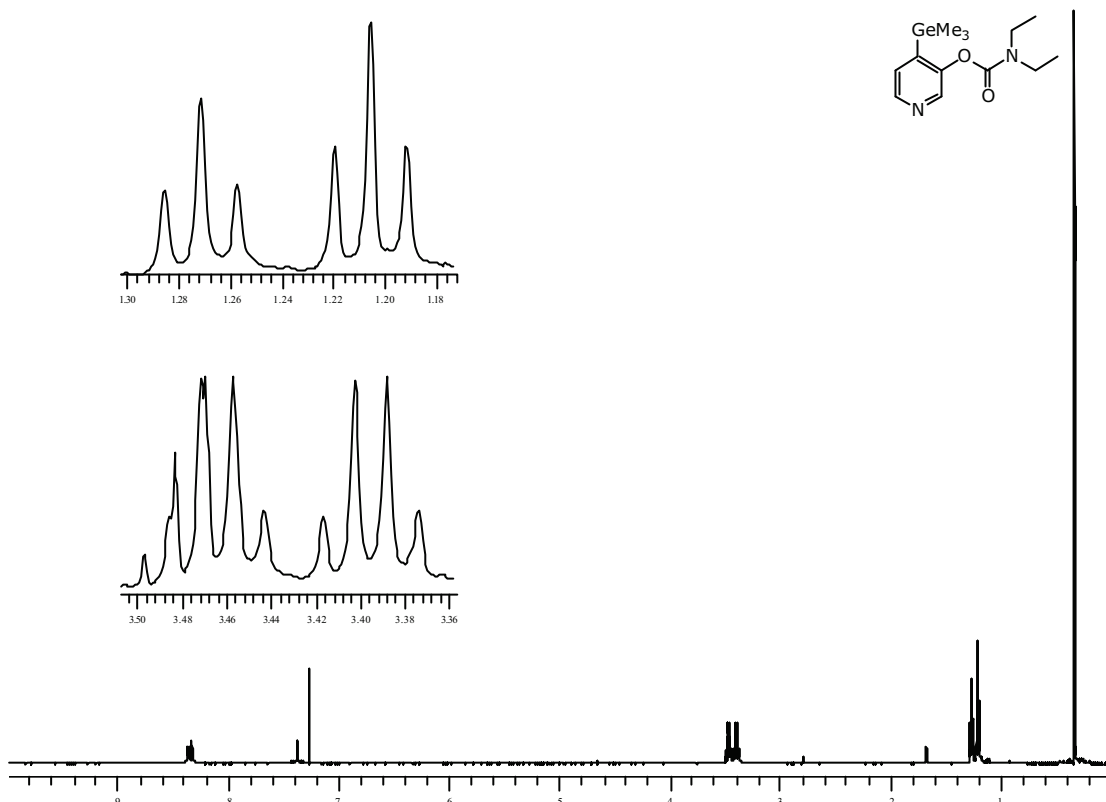


C₁₃H₂₂GeN₂O₂
 Exact Mass: 312.09
 Mol. Wt.: 310.94
 C, 50.22; H, 7.13; Ge, 23.35; N, 9.01; O, 10.29

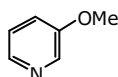
Snieckus' method of preparation of 3-Pyridyldiethylcarbamyl-4-trimethylstannane **110**^{129,130} was modified as follows: trimethylstannane chloride was replaced with trimethylgermanium bromide.

To a solution of freshly distilled TMEDA (330 μ L, 2.2 mmol) in THF (4 mL) at -78 °C was added a solution of *sec*-BuLi (1.3 M in hexanes, 1.7 mL, 2.2 mmol). The resultant bright yellow solution was left to stir for 1 h, after which a solution of *carbamate* **109** (200 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The resultant red solution was left to stir for a further 1 h. Trimethylgermanium bromide (0.13 μ L, 1.0 mmol) was added dropwise to the stirring solution. The reaction mixture was warmed to 25 °C over a period of 2 h. The reaction was concentrated *in vacuo* to give a golden, viscous oil. Purification by FC (CHCl₃ → CHCl₃/Et₂O, 50:50) afforded *germane* **111** (174 mg, 48%) as a pale yellow oil. *R*_f 0.39 (CHCl₃/Et₂O, 50:50); ν_{max} /cm⁻¹ (neat) 1720 (C=O), 1639, 1399 and 1270; δ_{H} (CDCl₃, 400 MHz) 0.40 (9H, s, GeCH₃), 1.18 (3H, t, *J* 7.0 Hz, CH₃CH₂), 1.22 (3H, t, *J* 7.0 Hz, CH₃CH₂), 3.37 (2H, q, *J* 7.0 Hz, CH₃CH₂), 3.41 (2H, q, *J* 7.0 Hz, CH₃CH₂), 7.31 (1H, d, *J* 4.5 Hz, CHCHCH), 8.33 (1H, s, NCHCO) and 8.39 (1H, d, *J* 4.5 Hz, NCHCH); δ_{C} (CDCl₃, 100 MHz) -1.6 (3q), 13.3 (q), 14.0 (q), 41.0 (t),

41.7 (t), 128.4 (d), 129.2 (s), 143.8 (d), 145.3 (d), 152.2 (s), 153.9 (s). MS (CI^+) m/z 313 (MH^+ , 100), 311 (80), 309 (70), 315 (40), 279 (40), 100 (30); HRMS (CI^+) calcd for $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_2^{74}\text{Ge}(\text{MH}^+)$ 313.0972, found 313.0974 ($? = + 0.2$ ppm).

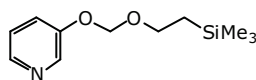


3-Methoxypyridine (**112**).¹³⁴



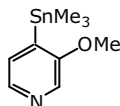
$\text{C}_6\text{H}_7\text{NO}$
Exact Mass: 109.05
Mol. Wt.: 109.13
C, 66.04; H, 6.47; N, 12.84; O, 14.66

To a solution of *3-hydroxypyridine* (1.00 g, 10.5 mmol) in DMF (15 mL) was added a suspension of NaH (0.52 g, 13.0 mmol, 60% suspension in oil) in DMF (15 mL). After stirring the reaction mixture for 1 h at 25 °C, iodomethane (1.91 g, 13.4 mmol) was added and left to stir for a further 3 h at 25 °C. The reaction mixture was quenched with HCl (1N, 66 mL) and washed with Et_2O (2 × 100 mL). The aqueous layer was basified with NaOH (1N, 100 mL, pH > 10) and then extracted with Et_2O (3 × 100 mL), the organic extracts washed with H_2O (3 × 100 mL), brine (100 mL), dried over MgSO_4 and concentrated *in vacuo* to afford *ether 112* (916 mg, 80%) as a yellow oil. R_f 0.32 ($\text{CHCl}_3/\text{Et}_2\text{O}$, 50:50); δ_{H} (CDCl_3 , 270 MHz) 3.78 (3H, s, CH_3), 7.15 (2H, bt, J 1.5 Hz CHCHCO), 8.16 (1H, d, J 1.5 Hz, NCHCH) and 8.26 (1H, d, J 1.5 Hz, NCHCO). MS (CI^+) m/z 110 (MH^+ , 100); HRMS (CI^+) calcd for $\text{C}_6\text{H}_8\text{NO}(\text{MH}^+)$ 110.0603, found 110.0606 ($? = - 0.3$ ppm).

3-(2-Trimethylsilanylethoxymethoxy)pyridine (113).^{132 181}

C₁₁H₁₉NO₂Si
 Exact Mass: 225.12
 Mol. Wt.: 225.36
 C, 58.63; H, 8.50; N, 6.22; O, 14.20; Si, 12.46

To a solution of *3-hydroxypyridine* (1.00 g, 10.5 mmol) in DMF (15 mL) was added a suspension of NaH (0.52 g, 13.0 mmol, 60% suspension in oil) in DMF (15 mL). After stirring the reaction mixture for 1 h at 25 °C, iodomethane (1.91 g, 13.4 mmol) was added and the reaction mixture left to stir for a further 3 h. The reaction mixture was quenched with HCl (1N, 66 mL) and the mixture was washed with Et₂O (2 × 100 mL). The aqueous layer was basified with NaOH (1N, 100 mL, pH > 10) and then extracted with Et₂O (3 × 100 mL), the organic extracts washed with H₂O (3 × 100 mL), brine (100 mL), dried over MgSO₄ and concentrated *in vacuo* to afford *ether 113* (2.27 g, 96%) as a pale yellow oil. *R*_f 0.32 (CHCl₃/Et₂O, 50:50); δ_{H} (CDCl₃, 270 MHz) -0.01 (9H, s, SiCH₃), 0.93 (2H, t, *J* 8.5 Hz, CH₂Si), 3.77 (2H, t, *J* 8.5, OCH₂CH₂), 5.26 (2H, s, OCH₂O), 7.20 (1H, dd, *J* 5.0 and 8.0 Hz, NCHCHCH), 7.20 (1H, dd, *J* 1.5 and 8.0 Hz, NCHCHCH), 8.26 (1H, d, *J* 4.0, NCHCH) and 8.41 (1H, d, *J* 2.5, NCHCO). MS (CI⁺) *m/z* 226 (MH⁺, 100), 90 (20); HRMS (CI⁺) calcd for C₁₁H₂₀NO₂Si (MH⁺) 226.1263, found 226.1272 (? = 0.9 ppm).

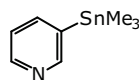
3-Methoxy-4-trimethylstannanylpyridine (114).¹³⁷

C₉H₁₅NOSn
 Exact Mass: 273.02
 Mol. Wt.: 271.93
 C, 39.75; H, 5.56; N, 5.15; O, 5.88; Sn, 43.65

To a solution of *methoxypyridine 112* (300 mg, 1.9 mmol) in Et₂O (8 mL) was added MeLi (1.6 M solution in pentane, 1.3 mL, 2.1 mmol) at 25 °C. The reaction mixture was left to stir for 1 h, after which SnMe₃Cl (378 mg, 1.9 mmol) in Et₂O (8 mL) was added and the reaction mixture was left to stir for a further 16 h at 25 °C. The reaction mixture was filtered to afford a white solid and a pale yellow solution; which was concentrated *in vacuo* to a yellow oil. Purification of the oil by FC (Et₂O/CHCl₃, 75:25) afforded *stannane 114* (1.84 g, 75%) as a pale yellow oil. *R*_f 0.36 (Et₂O/CHCl₃, 75:25); δ_{H} (CDCl₃, 500 MHz) 0.27 [9H, (83% ^{116,118,120,122,124}Sn), s; (17% ^{117,119}Sn), t, *J* 27.5 Hz, SnCH₃], 3.89 (3H, s, OCH₃), 7.28 (1H, d, *J* 4.0 Hz, CHCSn), 8.17 (1H, s, NCHCO) and 8.21 (1H, d, *J* 4.0 Hz, NCHCH); δ_{C} (CDCl₃, 125 MHz) -9.3 (3q), 55.9 (q), 130.9 (d), 131.4 (d), 140.5

(s), 142.3 (d) and 160.2 (s). MS (CI^+) m/z 274 (MH^+ , 100), 272 (80), 270 (50), 234 (50), 208 (40), 52 (50); HRMS (CI^+) calcd for $\text{C}_9\text{H}_{15}\text{NO}^{120}\text{Sn}$ (MH^+) 274.0254, found 274.0249 ($\delta = -0.5$ ppm).

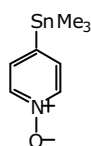
3-Trimethylstannanylpuridine (**116**).¹⁴⁰



$\text{C}_8\text{H}_{13}\text{NSn}$
Exact Mass: 243.01
Mol. Wt.: 241.91
C, 39.72; H, 5.42; N, 5.79; Sn, 49.07

To a solution of 3-bromopyridine (1.2 mL, 13.0 mmol) in THF (30 mL) at -78°C was added a solution of *t*-BuLi (1.5 M in pentane, 10.0 mL, 15.0 mmol). The reaction mixture was left to stir for 1 h, after which the trimethylstannane chloride (2.59 g, 13.0 mmol) dissolved in THF (5 mL) was added dropwise. The reaction mixture was warmed to room temperature over a period of 2 h. Reaction mixture was concentrated to a red oil. Purification by FC ($\text{Et}_2\text{O}/\text{CHCl}_3$, 50:50) afforded stannane **116** (314 mg, 10%) as a pale yellow oil. R_f 0.84 ($\text{Et}_2\text{O}/\text{CHCl}_3$, 50:50); δ_{H} (CDCl_3 , 300 MHz) 0.35 [9H, (83% $^{116,118,120,122,124}\text{Sn}$), s; (17% $^{117,119}\text{Sn}$), t, J 28.0 Hz, SnCH_3], 7.25 (1H, bd, J 1.5 Hz, CHCHCSn), 7.77 (1H, bd, J 1.5 Hz, NCHCH), 8.53 (1H, bd, J 1.5 Hz, NCHCH), and 8.63 (1H, s, NCHCSn). MS (CI^+) m/z 244 (MH^+ , 100), 213 (20), 182 (30), 157 (30), 95 (20), 80 (40); HRMS (CI^+) calcd for $\text{C}_8\text{H}_{14}\text{N}^{120}\text{Sn}$ (MH^+) 244.0148, found 244.0140 ($\delta = -3.3$ ppm).

4-Trimethylstannanylpuridine-*N*-oxide (**117**).¹²⁶

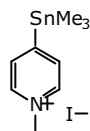


$\text{C}_8\text{H}_{13}\text{NOSn}$
Exact Mass: 259.00
Mol. Wt.: 257.90
C, 37.26; H, 5.08; N, 5.43; O, 6.20; Sn, 46.03

To a solution of stannane **106** (129 mg, 0.5 mmol) in chloroform (2.5 mL) at room temperature, in a foil covered flask was added *m*CPBA (57-86%, 175 mg, 0.6 mmol). The reaction mixture was left to stand in the dark for 72 h. The reaction mixture was concentrated to afford a white solid. Purification by reverse phase C18 FC ($\text{Et}_2\text{O} \rightarrow \text{CHCl}_3/\text{Et}_2\text{O}$, 50:50) afforded *N*-oxide **117** (101 mg, 74%) as a white solid. R_f 0.23 ($\text{MeCN}/\text{H}_2\text{O}$, 91:9); mp $193\text{--}195^\circ\text{C}$ (Et_2O) [Lit.,¹²⁶ 194°C (Et_2O)]; δ_{H} (CDCl_3 , 300 MHz) 0.37 [9H, (83% $^{116,118,120,122,124}\text{Sn}$), s; (17% $^{117,119}\text{Sn}$), t, J 28.0 Hz, SnCH_3], 7.42 (2H, broad s, CHCSn) and 8.16 (2H, broad

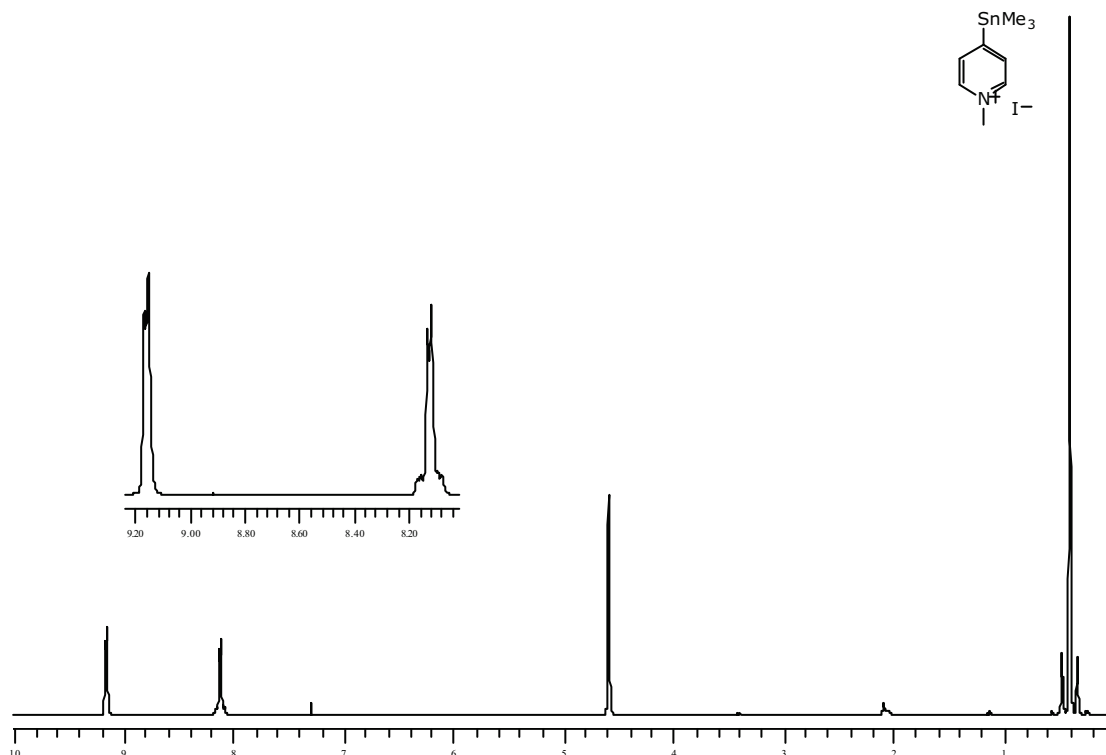
s, NCH). δ_{C} (CDCl_3 , 100 MHz) -9.4 (3q), 133.1 (2d), 137.9 (2d) and 143.2 (s). MS (CI^+) m/z 260 (MH^+ , 100); HRMS (CI^+) calcd for $\text{C}_8\text{H}_{14}\text{NO}^{120}\text{Sn}$ (MH^+) 260.0101, found 260.0105 ($\delta = 0.4$ ppm).

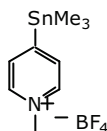
***N*-Methyl-4-trimethylstannanylpyridinium; iodide (118).**



$\text{C}_9\text{H}_{16}\text{INSn}$
 Exact Mass: 384.93
 Mol. Wt.: 383.84
 C, 28.16; H, 4.20; I, 33.06; N, 3.65; Sn, 30.93

To a solution of *stannane* **106** (100 mg, 0.4 mmol) in MeCN (1 mL) was added methyl iodide (128 μL , 2.1 mmol) in one portion. The reaction mixture was left to stir at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* to afford *methyl iodide salt* **118** (110 mg, 94%) as a amorphous white solid. R_f 0.05 (MeCN/ H_2O , 89:11); ν_{max} / cm^{-1} (neat) 1211 and 1181; δ_{H} (d_6 -acetone, 400 MHz) 0.49 [9H, (83% $^{116,118,120,122,124}\text{Sn}$), s; (17% $^{117,119}\text{Sn}$), t, J 29.0 Hz, SnCH_3], 4.59 (3H, s, NCH_3), 8.40 (2H, d, J 6.0 Hz, CHCSn) and 9.02 (2H, d, J 6.0 Hz, NCH); δ_{C} (d_6 -acetone, 125 MHz) -8.7 (3q), 48.7 (q), 136.0 (2d), 142.8 (2d) and 171.7 (s); MS ($\pm\text{FAB}$) m/z ; 127 (I^- , 100), 256 ($\text{C}_9\text{H}_{16}\text{NSn}^+$, 100).

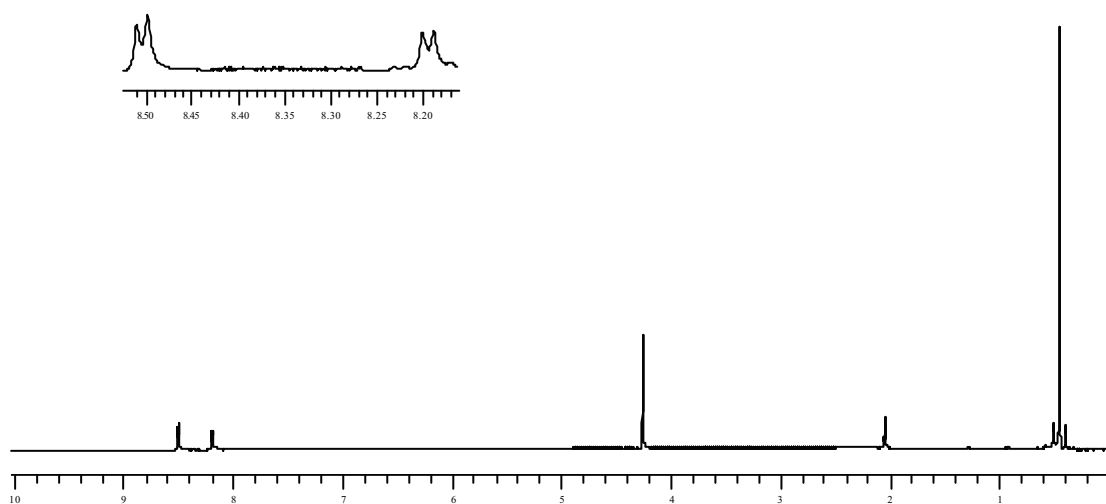
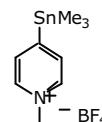


N-Methyl-4-trimethylstannanylpyridinium; tetrafluoro borate (119).

C₉H₁₆BF₄NSn
 Exact Mass: 345.03
 Mol. Wt.: 343.74

C, 31.45; H, 4.69; B, 3.15; F, 22.11; N, 4.07; Sn, 34.53

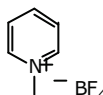
To a solution of *stannane* **118** (50 mg, 0.1 mmol) in MeCN (1 mL) was added silver tetrafluoroborate (28 mg, 0.1 mmol) in one portion. The reaction mixture was left to stir at room temperature over night. The reaction mixture was concentrated *in vacuo* to afford *methyl tetrafluoroborate salt* **119** (41 mg, 92%) as a white crystalline solid. *R_f* 0.21 (MeCN/H₂O, 85:15); mp 210-212 °C (acetone); ν_{max} (KBr) 1061 (BF₄) and 1031 (BF₄); δ_{H} (CDCl₃, 270 MHz) 0.39 [9H, (83% ^{116,118,120,122,124}Sn), s; (17% ^{117,119}Sn), t, *J* 29.0 Hz, SnCH₃], 4.57 (3H, s, NCH₃), 8.10 (2H, d, *J* 6.0 Hz, SnCCH) and 8.49 (2H, d, *J* 6.0 Hz, NCH); δ_{C} (*d*₆-acetone, 125 MHz) sample unstable; MS ($\pm$ FAB) *m/z*; 87 (BF₄⁻, 100), 256 (C₉H₁₆NSn⁺, 100).



N-Methylpyridinium; iodide (122).¹²⁷

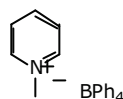
C₆H₈IN
 Exact Mass: 220.97
 Mol. Wt.: 221.04
 C, 32.60; H, 3.65; I, 57.41; N, 6.34

To a solution of *pyridine* (500 mg, 6.3 mmol) in Et₂O (2 mL) was added methyl iodide (472 μ L, 7.6 mmol) in one portion. The reaction mixture was left to stir at room temperature for 2 h at which time a heavy white precipitate was observed. The reaction mixture was concentrated *in vacuo* to afford *methyl iodide salt 122* (1.24 g, 89%) as a white microcrystalline solid. *R_f* 0.29 (MeCN/H₂O, 90:10); mp: 116-118 °C (H₂O) [Lit.,¹²⁷ 117 °C (H₂O)]; δ_{H} (*d*₆-DMSO, 500 MHz) 4.36 (3H, s, CH₃), 8.13 (2H, collapsed t, *J* 7.0 Hz, NCHCH), 8.58 (1H, t, *J* 8.0 Hz, CHCHCH) and 9.00 (2H, d, *J* 6.0 Hz, NCH); δ_{C} (*d*₆-DMSO, 125 MHz) 48.0 (q), 127.6 (d), 145.0 (2d) and 145.4 (2d); MS ($\pm$ FAB) *m/z*; 127 (I, 100), 94 (C₆H₈N⁺, 100).

N-Methylpyridinium; tetrafluoroborate (123).¹²⁷

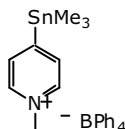
C₆H₈BF₄N
 Exact Mass: 181.07
 Mol. Wt.: 180.94
 C, 39.83; H, 4.46; B, 5.97; F, 42.00; N, 7.74

To a solution of *iodide 122* (2.00 g, 9.0 mmol) in MeCN (20 mL) was added sodium tetrafluoroborate (1.19 g, 10.9 mmol) in one portion. The reaction mixture was left to stir at room temperature for overnight at which time a heavy white precipitate was observed. The reaction mixture was concentrated *in vacuo* and the residue was recrystallised from MeCN to afford *methyl tetrafluoroborate salt 123* (1.38 g, 85%) as a white microcrystalline solid. *R_f* 0.27 (MeCN/H₂O, 85:15); mp 128-130 °C (H₂O); ν_{max} /cm⁻¹ (KBr) 1058 (BF₄) and 1031 (BF₄); δ_{H} (*d*₆-DMSO, 500 MHz) 4.35 (3H, s, CH₃), 8.12 (2H, t, *J* 7.0 Hz, NCHCH), 8.57 (1H, collapsed t, *J* 8.0 Hz, CHCHCH) and 8.98 (2H, d, *J* 6.0 Hz, NCH); δ_{C} (*d*₆-DMSO, 125 MHz) 47.9 (q), 127.6 (d), 145.0 (2d) and 145.4 (2d); MS ($\pm$ FAB) *m/z*; 87 (BF₄⁻, 100), 94 (C₆H₈N⁺, 100).

N-Methylpyridinium; tetraphenylborate (124).¹²⁷

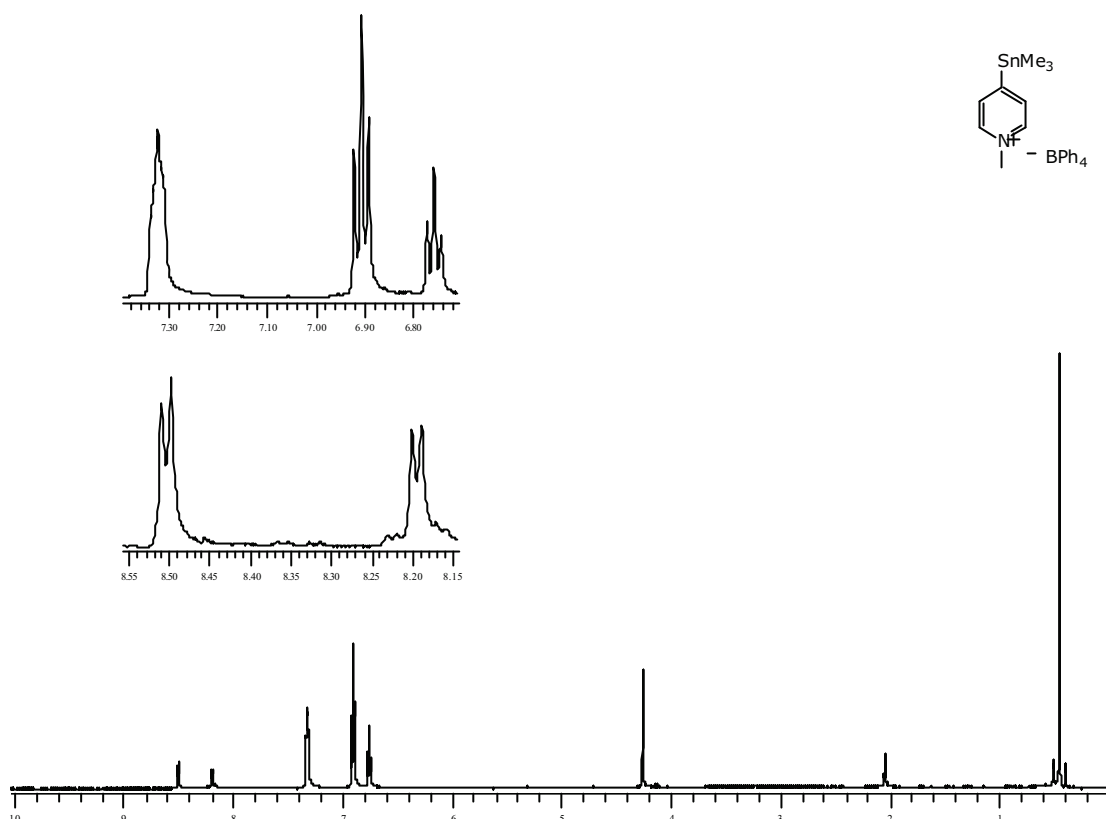
C₃₀H₂₈BN
 Exact Mass: 413.23
 Mol. Wt.: 413.36
 C, 87.17; H, 6.83; B, 2.62; N, 3.39

To a solution of *iodide 122* (1.00 g, 4.5 mmol) in MeCN (10 mL) was added sodium tetrafluoroborate (1.69 g, 5.0 mmol) in one portion. The reaction mixture was left to stir at room temperature for over night at which time a heavy white precipitate was observed. The reaction mixture was concentrated *in vacuo* and the residue was recrystallised from MeCN to afford methyl tetraphenylborate salt **124** (1.68 g, 90%) as a white microcrystalline solid. *R_f* 0.27 (MeCN/H₂O, 80:20); mp 141-143 °C (H₂O); $\nu_{\max}/\text{cm}^{-1}$ (KBr) 1438, 1411 and 1212; δ_{H} (*d*₆-acetone, 270 MHz) 4.35 (3H, s, CH₃), 6.75 (8H, m, Ar-H), 6.95 (4H, m, Ar-H), 7.30 (8H, broad s, Ar-H), 8.05 (2H, broad s, NCHCH), 8.52 (1H, t, *J* 7.5 Hz, CHCHCH) and 8.87 (2H, d, *J* 6.0, NCH). δ_{C} (*d*₆-DMSO, 100 MHz) 48.0 (q), 121.5 (8d), 125.3 (8d), 127.7 (4s), 135.6 (4d), 145.0 (2d) and 145.5 (2d), 163.2 (s); MS ($\pm$ FAB) *m/z*; 319 (BPh₄⁻, 100), 94 (C₆H₈N⁺, 100).

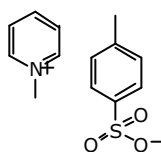
N-Methyl-4-trimethylstannanylp pyridinium; tetraphenylborate (125).

C₃₃H₃₆BN₂Sn
 Exact Mass: 577.20
 Mol. Wt.: 576.17
 C, 68.79; H, 6.30; B, 1.88; N, 2.43; Sn, 20.60

To a solution of *iodide 118* (50 mg, 0.1 mmol) in MeCN (1 mL) was added silver tetraphenylborate (49 mg, 0.1 mmol) in one portion. The reaction mixture was left to stir at room temperature over night. The reaction mixture was concentrated *in vacuo* to afford *methyl tetraphenylborate salt 125* (67 mg, 89%) as an amorphous solid. *R_f* 0.20 (MeCN/H₂O, 85:15); δ_{H} (*d*₆-acetone, 500 MHz) 0.45 [9H, (83% ^{116,118,120,122,124}Sn), s; (17% ^{117,119}Sn), t, *J* 30.0 Hz, SnCH₃], 4.25 (3H, s, CH₃), 6.75 (4H, t, *J* 7.0 Hz, CH₃CH₂), 6.90 (10H, t, *J* 7.0 Hz, CH₃CH₂), 7.32 (10H, broad s, Ar-H), 8.19 (2H, d, *J* 6.0 Hz, NCHCH) and 8.50 (2H, d, *J* 6.0 Hz, NCH). δ_{C} (*d*₆-acetone, 125 MHz) -8.8 (3q), 48.3 (q), 122.2 (8d), 126.0 (8d), 135.8 (4s), 136.8 (4d), 142.4 (2d), 165.0 (2d) and 173.1 (s); MS ($\pm$ FAB) *m/z*; 319 (BPh₄⁻, 100), 258 (C₉H₁₆NSn⁺, 100).



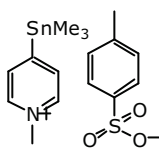
***N*-Methyl-pyridinium; toluene-4-sulfonate (**126**).¹²⁷**



$C_{13}H_{15}NO_3S$
Exact Mass: 265.08
Mol. Wt.: 265.33

C, 58.85; H, 5.70; N, 5.28; O, 18.09; S, 12.09

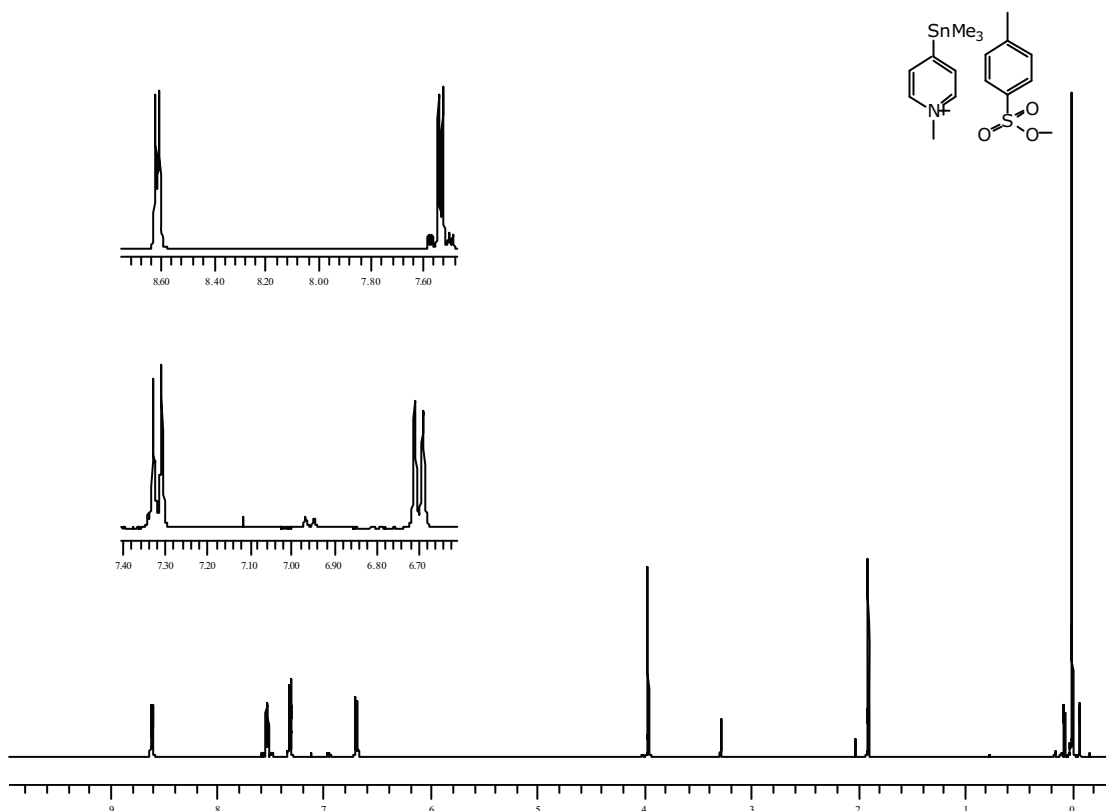
To a solution of *pyridine* (1 mL, 12.0 mmol) in Et_2O (5 mL) was added methyl tosylate (3.35 g, 18.0 mmol) in one portion. The reaction mixture was left to stir at room temperature for over night at which time a heavy white precipitate was observed. The reaction mixture was concentrated *in vacuo* and the residue was recrystallised from MeCN to afford *methyl tosylate salt* **126** (1.68 g, 90%) as a white amorphous solid. R_f 0.18 (MeCN/ H_2O , 85:15); ν_{max}/cm^{-1} (KBr) 1438, 1411 and 1212; δ_H ($CDCl_3$, 270 MHz) 2.28 (3H, s, CH_3), 4.35 (3H, s, NCH_3), 7.10 (2H, d, J 8.0 Hz, CH_3CH), 7.46 (2H, d, J 11.5 Hz, $SCCH$), 8.09 (2H, t, J 7.0 Hz, $NCHCH$), 8.55 (1H, t, J 8.0 Hz, $NCHCHCH$) and 8.99 (2H, d, J 6.0 Hz, NCH). δ_C ($CDCl_3$, 100 MHz) 20.7 (q), 48.1 (q), 125.4 (2d), 127.7 (2d), 128.3 (2d), 138.9 (s), 143.5 (s), 144.4 (2d) and 145.5 (d); MS ($\pm$ FAB) m/z ; 171 (OTs^- , 100, 94 ($C_6H_8N^+$, 100).

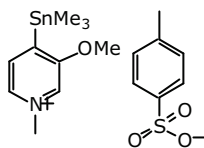
N-Methyl-4-trimethylstannanylpipridinium; toluene-4-sulfonate (127).

C₁₆H₂₃NO₃SSn
Exact Mass: 429.04
Mol. Wt.: 428.13

C, 44.89; H, 5.41; N, 3.27; O, 11.21; S, 7.49; Sn, 27.73

To a solution of *stannane* **106** (200 mg, 0.8 mmol) in Et₂O (1 mL) was added methyl tosylate (170 mg, 0.9 mmol) in one portion. The reaction mixture was left to stir at room temperature for over night at which time a heavy white precipitate was observed. The reaction mixture was concentrated *in vacuo* and the residue was recrystallised from MeCN to afford *methyl tosylate salt* **127** (274 mg, 80%) as a white hygroscopic solid. *R*_f 0.06 (MeCN/H₂O, 90:10); $\nu_{\max}$ /cm⁻¹ (Neat) 3442, 2923, 2134, 1625, 1557, 1444, 1327, 1189, 1124, 1036 and 1012; δ_{H} (CDCl₃, 500 MHz) 0.04 [9H, (83% ^{116,118,120,122,124}Sn), s; (17% ^{117,119}Sn), t, *J* 55.0 Hz, SnCH₃], 2.03 (3H, s, CH₃), 3.97 (3H, s, NCH₃), 6.70 (2H, d, *J* 10 Hz, CH₃CH), 7.34 (2H, d, *J* 10 Hz, SCCH), 7.54 (2H, d, *J* 7.5 Hz, NCHCH) and 8.61 (2H, d, *J* 7.5 Hz, NCH); δ_{C} (CDCl₃, 125 MHz) -9.70 (3q), 20.6 (q), 47.1 (q), 125.1 (2d), 129.3 (2d), 134.32 (s), 138.4 (s), 141.5 (s), 143.43 (2d) and 168.4 (2d); MS ($\pm$ FAB) *m/z*; 171 (OTs⁻, 100), 258 (C₉H₁₆NSn⁺, 100).

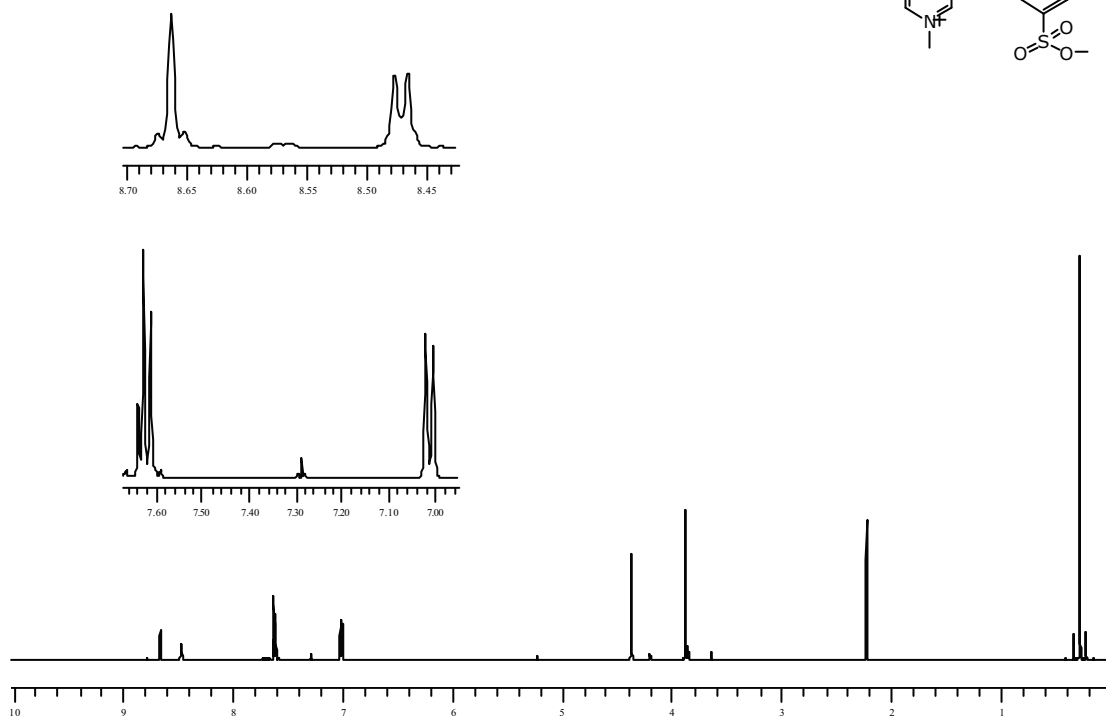
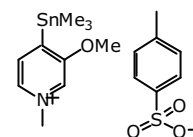


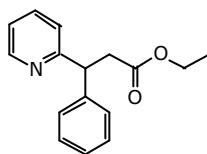
3-Methoxy-*N*-methyl-4-trimethylstannanylpipridinium; toluene-4-sulfonate (131).


C₁₇H₂₅NO₄SSn
Exact Mass: 459.05
Mol. Wt.: 458.16

C, 44.57; H, 5.50; N, 3.06; O, 13.97; S, 7.00; Sn, 25.91

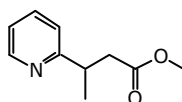
To a solution of *stannane* **114** (200 mg, 0.83 mmol) in Et₂O (1 mL) was added methyl tosylate (154 mg, 0.83 mmol) in one portion. The reaction mixture was left to stir at room temperature for over night at which time a heavy white precipitate was observed. The reaction mixture was concentrated *in vacuo* and the residue was recrystallised from MeCN to afford *methyl tosylate salt* **131** (361 mg, 95%) as a white amorphous solid. *R*_f 0.06 (Et₂O); $\nu_{\max}$ /cm⁻¹ (Neat) 3448, 2073, 1639, 1487, 1438, 1319 and 1192; δ_{H} (CDCl₃, 500 MHz) 0.28 [9H, (83% ^{116,118,120,122,124}Sn), s; (17% ^{117,119}Sn), t, *J* 29.0 Hz, SnCH₃], 2.23 (3H, s, PhCH₃), 3.88 (3H, s, NCH₃), 4.37 (3H, s, OMe), 7.01 (2H, d, *J* 8.0 Hz, 2 × CH₃CH), 7.60–7.64 (3H, m, NCHCH and 2 × SO₂CCH), 8.46 (1H, d, *J* 5.5 Hz, NCHCH) and 8.66 (1H, bs, NCH); δ_{C} (CHCl₃, 125 MHz) –8.9 (q), 21.2 (q), 48.3 (q), 57.8 (q), 125.7 (d), 125.9 (d), 128.6 (d), 134.2 (d), 136.7 (d), 139.2 (s), 143.7 (s), 155.3 (s) and 162.9 (s); MS (±FAB) *m/z*; 171 (OTs⁻, 100), 288 (C₁₀H₁₈NOSn⁺, 100).



(±)-Phenyl-3-pyridin-2-ylpropionic acid ethyl ester (33).⁴⁸

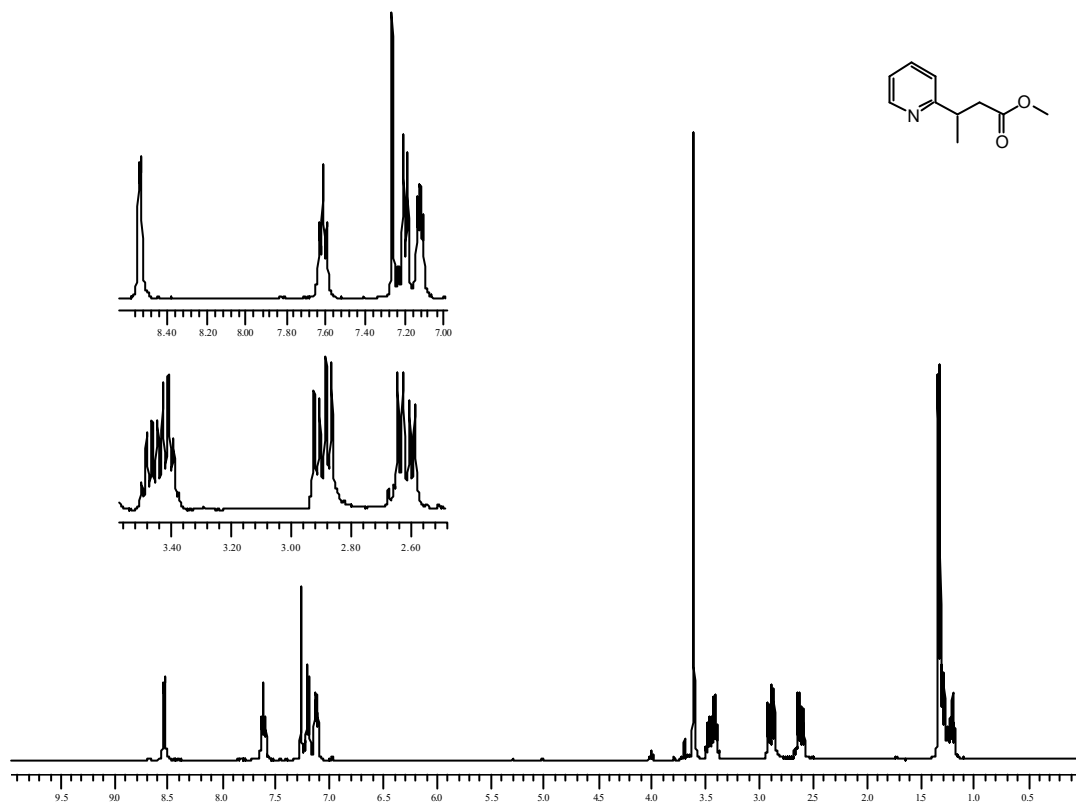
C₁₆H₁₇NO₂
 Exact Mass: 255.13
 Mol. Wt.: 255.31
 C, 75.27; H, 6.71; N, 5.49; O, 12.53

According to the method of Nilsson⁴⁸ a solution of BuLi (1.74 M in hexanes, 6.3 mL, 11.0 mmol) was added to a solution of 2-bromopyridine (1.74 g, 11.0 mmol) in Et₂O (10 mL) at -78 °C and the deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (1.05 g, 5.5 mmol) in dibutylsulfide (1.9 mL, 11.0 mmol) and Et₂O (15 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of ethyl *trans*-cinnamate (3.7 mL, 22.0 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (5 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 × 50 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 100 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by distillation (198-203 °C/0-5 mmHg) afforded ester **33** (1.12 g, 80%) as a colourless oil. *R*_f 0.61 (Et₂O/CHCl₃, 1:3); ν_{max} /cm⁻¹ (neat) 1729 (C=O), 1591, 1434 and 1266; δ_{H} (CDCl₃, 400 MHz) 1.13 (3H, t, *J* 7.0 Hz, CH₃), 2.97 (1H, dd, *J* 16.0 and 7.0 Hz, CH₂), 3.44 (1H, dd, *J* 16.0 and 7.0 Hz, CH₂), 4.04 (2H, q, *J* 7.0 Hz, CH₃CH₂), 4.64 (1H, t, *J* 7.0 Hz, CH), 7.06-7.38 (7H, ArCH), 7.53 (1H, bt, *J* 7.0 Hz, NCHCHCH) and 8.55 (1H, bd, *J* 5.0 Hz, NCH). δ_{C} (CDCl₃, 100 MHz) 14.1 (q), 39.7 (t), 49.0 (d), 60.3 (t), 121.2 (d), 123.9 (d), 126.5 (d), 127.9 (2d), 128.8 (2d), 136.3 (d), 142.7 (s), 149.0 (d), 162.0 (s) and 172.3 (s); MS (CI⁺) *m/z* 256 (MH⁺, 100), 213 (30), 182 (30), 167 (30); HRMS (CI⁺) calcd for C₁₆H₁₇NO₂ (MH⁺) 256.1324, found 256.1329 (? = + 0.5 ppm).

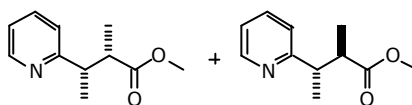
(±)-3-Pyridin-2-yl butyric acid methyl ester (135).

C₁₀H₁₃NO₂
 Exact Mass: 179.09
 Mol. Wt.: 179.22
 C, 67.02; H, 7.31; N, 7.82; O, 17.85

To a solution of 2-bromopyridine (1.74 g, 11.0 mmol) in Et₂O (20 mL) at -78 °C was added a solution of BuLi (1.74 M in hexanes, 6.3 mL, 11.0 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (1.05 g, 5.5 mmol) in dibutylsulfide (1.9 mL, 11.0 mmol) and Et₂O (15 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of methyl crotonate (2.3 mL, 22.0 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (5 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 × 50 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 100 mL, 2 M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by distillation (212-218 °C/0-5 mmHg) then FC (Et₂O/CHCl₃, 50:50) afforded ester **135** (778 mg, 79%) as a colourless oil. *R*_f 0.42 (Et₂O/CHCl₃, 75:25); ν_{max} /cm⁻¹ (neat) 1732 (C=O), 1593, 1436 and 1269; δ_{H} (CDCl₃, 400 MHz) 1.32 (3H, d, *J* 7.0 Hz, CH₃CH), 2.61 (1H, dd, *J* 16.0 and 7.0 Hz, CH₂), 2.89 (1H, dd, *J* 16.0 and 7.0 Hz, CH₂), 3.41 (1H, m, PyCH), 3.61 (3H, s, OCH₃), 7.11 (1H, bt, *J* 5.0 Hz, NCHCH), 7.19 (1H, *J* 7.5 Hz, NCHCH), 7.61 (1H, bt, *J* 7.5 Hz, CHCHCH) and 8.54 (1H, d, *J* 5.0 Hz, NCH); δ_{C} (CDCl₃, 100 MHz) 20.9 (q), 38.0 (d), 40.5 (t), 51.5 (q), 121.5 (d), 122.0 (d), 136.6 (d), 149.1 (d), 164.2 (s) and 173.1 (s); MS (CI⁺) *m/z* 180 (MH⁺, 100), 148 (30), 120 (20); HRMS (CI⁺) calcd for C₁₀H₁₄NO₂ (MH⁺) 180.1025, found 180.1030 (? = + 0.5 ppm).



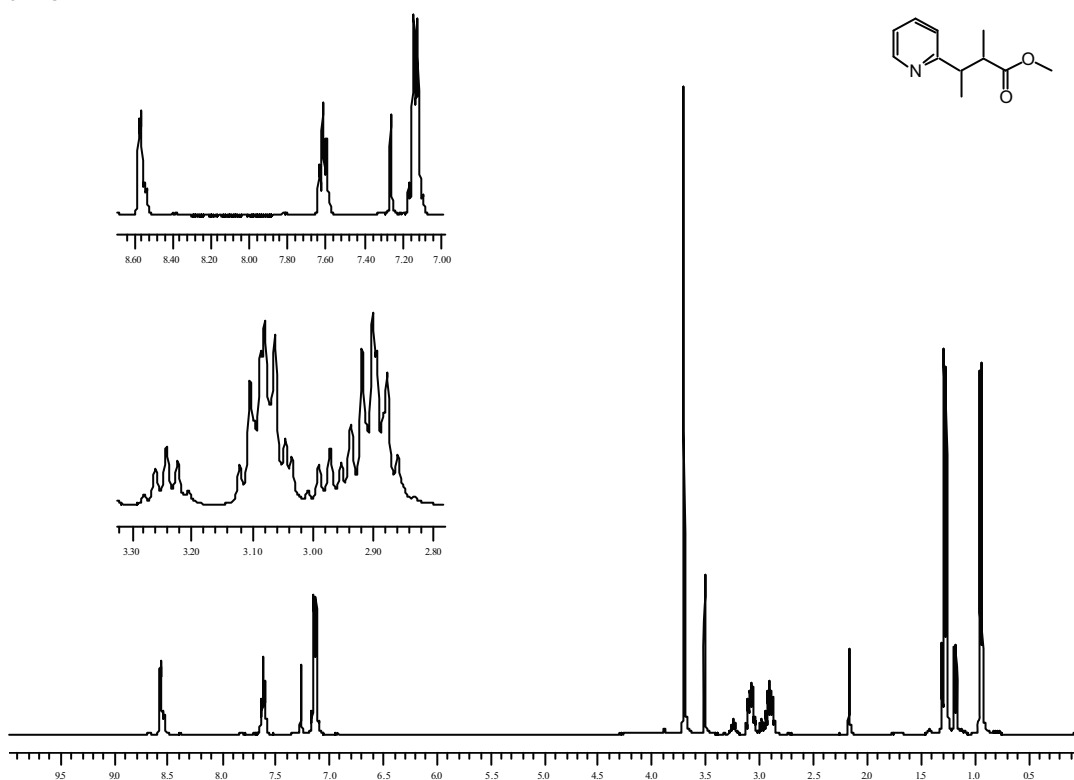
(±)-*syn*-2-Methyl-3-pyridin-2-yl butyric acid methyl ester (136a) and
(±)-*anti*-2-methyl-3-pyridin-2-yl butyric acid methyl ester (136b)



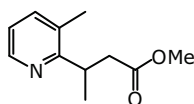
$C_{11}H_{15}NO_2$
 Exact Mass: 193.11
 Mol. Wt.: 193.24
 C, 68.37; H, 7.82; N, 7.25; O, 16.56

To a solution of *2-bromopyridine* (1.74 g, 11.0 mmol) in Et_2O (20 mL) at $-78\text{ }^{\circ}C$ was added a solution of BuLi (1.74 M in hexanes, 6.3 mL, 11.0 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (1.05 g, 5.5 mmol) in dibutylsulfide (1.9 mL, 11.0 mmol) and Et_2O (15 mL) at $0\text{ }^{\circ}C$. The resulting dark solution was stirred for 15 min at room temperature before addition of methyl tiglate (2.3 mL, 22.0 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (5 mL) was added and the phases separated. The aqueous layer was extracted with Et_2O ($3 \times 50\text{ mL}$). The organic extracts were combined and extracted with aqueous HCl ($2 \times 100\text{ mL}$, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et_2O ($3 \times 100\text{ mL}$). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow oil. Purification by distillation ($201\text{--}205\text{ }^{\circ}C/0\text{--}5\text{ mmHg}$), then FC ($Et_2O/CHCl_3$, 1:3) afforded *esters*

136a and **136b** (733 mg, 69%, 20:80, **136a:136b** by ^1H NMR) as a colourless oil. R_f 0.60 ($\text{CHCl}_3/\text{Et}_2\text{O}$, 3:1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1731 ($\text{C}=\text{O}$), 1594, 1436 and 1266; δ_{H} (CDCl_3 , 400 MHz) **Major**: 0.94 (3H, d, J 7.0 Hz, CH_3CHC), 1.26 (3H, d, J 7.0 Hz, CH_3CHCO), 2.89 (1H, m, CHCO_2CH_3), 3.08 (1H, m, PyCH), 3.70 (3H, s, OCH_3), 7.13 (2H, m, NCHCH), 7.61 (1H, m, NCHCHCH) and 8.55 (1H, m, NCH); **Minor**: 1.02 (3H, d, J 7.0 Hz, CH_3CHC), 1.29 (3H, d, J 7.0 Hz, CH_3CHCO), 2.93 (1H, m, CHCO_2CH_3), 3.12 (1H, m, PyCH), 3.74 (3H, s, OCH_3), 7.13 (2H, m, NCHCH), 7.61 (1H, m, CHCHCH) and 8.55 (1H, m, NCH). δ_{C} (CDCl_3 , 100 MHz) 16.1 (q), 19.2 (q), 44.7 (d), 45.3 (d), 51.4 (q), 121.6 (d), 122.9 (d), 136.5 (d), 149.3 (d), 163.4 (s) and 176.7 (s); MS (CI^+) m/z 194 (MH^+ , 100), 180 (50), 157 (5); HRMS (CI^+) calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_2$ (MH^+) 194.1181, found 194.1182 ($\Delta = +0.1$ ppm).



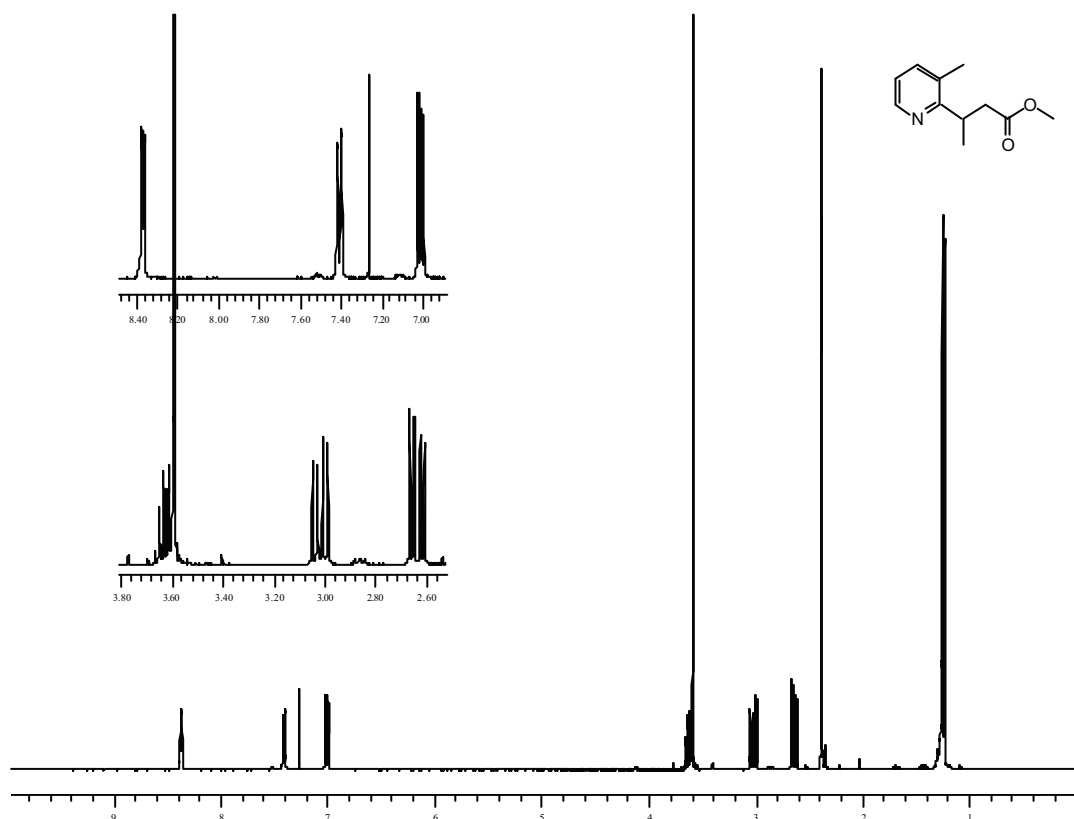
(±)-3-(3-Methylpyridin-2-yl) butyric acid methyl ester (138)

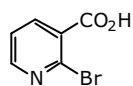


$\text{C}_{11}\text{H}_{15}\text{NO}_2$
 Exact Mass: 193.11
 Mol. Wt.: 193.24
 C, 68.37; H, 7.82; N, 7.25; O, 16.56

To a solution of 2-bromo-3-methylpyridine (1.3 mL, 11.0 mmol) in Et_2O (20 mL) at -78°C was added a solution of BuLi (2.39 M in hexanes, 4.6 mL, 11.0 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into

a solution of copper(I) iodide (1.05 g, 5.5 mmol) in dibutylsulfide (1.9 mL, 11.0 mmol) and Et₂O (15 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of methyl crotonate (2.3 mL, 22.0 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (5 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 × 50 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 100 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by distillation (211–221 °C/0–5 mmHg) then FC (Et₂O/CHCl₃, 1:3) afforded ester **138** (733 mg, 70%) as a colourless oil. *R*_f 0.54 (CHCl₃/Et₂O, 3:1); ν_{max} /cm⁻¹ (neat) 1736 (C=O), 1575, 1450 and 1437; δ_{H} (CDCl₃, 500 MHz) 1.21 (3H, d, *J* 7.0 Hz, CH₃CH), 2.37 (3H, s, CCH₃), 2.62 (1H, dd, *J* 16.0 and 7.0 Hz, CH₂), 2.99 (1H, dd, *J* 16.0 and 7.0 Hz, CH₂), 3.57 (3H, s, OCH₃), 3.60 (1H, m, PyCH), 6.99 (1H, m, NCHCH), 7.38 (1H, d, *J* 7.0 Hz, CHCHCH) and 8.38 (1H, d, *J* 5.0 Hz, NCH); δ_{C} (CDCl₃, 125 MHz) 18.6 (d), 20.2 (q), 22.1 (q), 39.9 (t), 51.5 (q), 121.1 (d), 130.3 (s), 137.8 (d), 146.6 (d), 162.5 (s) and 173.5 (s); MS (CI⁺) *m/z* 194 (MH⁺, 100), 162 (10), 134 (5); HRMS (CI⁺) calcd for C₁₁H₁₆NO₂ (MH⁺) 194.1181, found 194.1186 (δ = + 0.5 ppm).

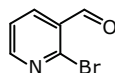


2-Bromonicotinic acid (140)¹⁵⁰

C₆H₄BrNO₂
Exact Mass: 200.94
Mol. Wt.: 202.01

C, 35.67; H, 2.00; Br, 39.56; N, 6.93; O, 15.84

To a suspension of *2-bromo-3-methylpyridine* (1.0 g, 6.0 mmol) in H₂O (25 mL) at room temperature was added KMnO₄ (2.4 g, 15.0 mmol) and the resulting solution was heated at reflux for 20 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to ~20 mL. This clear solution was acidified to pH 3 with aqueous HCl (1 M) and the resulting precipitate was collected by filtration and dried *in vacuo* to afford *nicotinic acid* **140** (1.2 g, 98%) as a white amorphous solid. *R*_f 0.35 (H₂O/CH₃CN, 1:9); ν_{max} /cm⁻¹ (neat) 3100, 2750, 2450, 1720 and 1575; δ_{H} (*d*₆-DMSO, 270 MHz) 7.55 (1H, dd, *J* 8.0 and 4.5 Hz), 8.10 (1H, dd, *J* 8.0 and 2.0 Hz), 8.45 (1H, dd, *J* 8.0 and 2.0 Hz) and 9.88 (1H, bs, COOH); MS (CI⁺) *m/z* 202 (MH⁺, 100), 204 (MNH₄⁺, 50), 221 (MNH₄⁺, 50); HRMS (CI⁺) calcd for C₆H₅⁷⁹BrNO₂ (MH⁺) 201.9504, found 201.9502 (? = - 0.2 ppm).

2-Bromopyridine-3-carbaldehyde (141)^{182, 150}.

C₆H₄BrNO
Exact Mass: 184.95
Mol. Wt.: 186.01

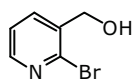
C, 38.74; H, 2.17; Br, 42.96; N, 7.53; O, 8.60

Method 1: According to the method of Melnyk,¹⁸² a solution of LDA was prepared by the dropwise addition of a solution of *n*-BuLi (1.75 M in hexanes, 1.9 mL, 3.3 mmol) to a solution of *i*-Pr₂NH (561 μ L, 4.0 mmol) in THF (10 mL) at -78 °C, followed by warming to 0 °C for 1 h. This solution was cooled to -78 °C and freshly distilled *2-bromopyridine* (286 μ L, 3.0 mmol) was added dropwise. After stirring for 4 h at -78 °C, freshly distilled DMF (2 mL) was added dropwise and the reaction mixture was left to stir for a further 30 min at -78 °C before being warmed to room temperature over 2 h. Saturated aqueous NH₄Cl (10 mL) was added to the reaction mixture and the resulting mixture extracted with Et₂O (3 $\times$ 20 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to yield a red oil. Purification by FC (hexane/EtOAc, 9:1) afforded *aldehyde* **141** (558 mg, 72%) as a white crystalline solid. mp 65 °C [*cf.* lit.¹⁸² 64-65°C]; *R*_f 0.19 (hexane/EtOAc, 9:1); ν_{max} /cm⁻¹ (neat) 3000, 1690 (C=O), 1573, 1557 and 1372; δ_{H} (CDCl₃, 270 MHz) 7.44 (1H, dd, *J* 8.0 and 4.5 Hz, NCHCHCH), 8.18 (1H, dd, *J* 8.0 and 2.0 Hz, NCHCHCH), 8.60 (1H, dd, *J* 4.5 and 2.0 Hz, NCH) and 10.35 (1H, s, CHO); MS (CI⁺) *m/z* 186

(MH^+ , 100), 102 (40); HRMS (CI^+) calcd for $\text{C}_6\text{H}_5^{79}\text{BrNO}$ (MH^+) 185.9555, found 185.9553 ($\delta = -0.2$ ppm).

Method 2: According to the method of Ashimori¹⁵⁰ a solution of *alcohol* **144** (200 mg, 1.0 mmol) and *N,N'*-dicyclohexylcarbodiimide (645 mg, 3.1 mmol) in DMSO (2.5 mL) was added anhydrous H_3PO_4 (1.0 M, 500 μL) and the mixture was stirred at room temperature for 1.5 h. The precipitate was filtered off and the filtrate diluted with H_2O (5 mL) and extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine, dried over MgSO_4 and concentrated *in vacuo* to afford a fluffy off-white solid. Purification by FC (hexane/ EtOAc , 9:1) afforded *aldehyde* **141** (158 mg, 80%) as a white crystalline solid. Spectroscopic data as above.

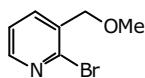
(2-Bromopyridin-3-yl) methanol (144**)**¹⁵⁰



$\text{C}_6\text{H}_6\text{BrNO}$
Exact Mass: 186.96
Mol. Wt.: 188.02

C, 38.33; H, 3.22; Br, 42.50; N, 7.45; O, 8.51

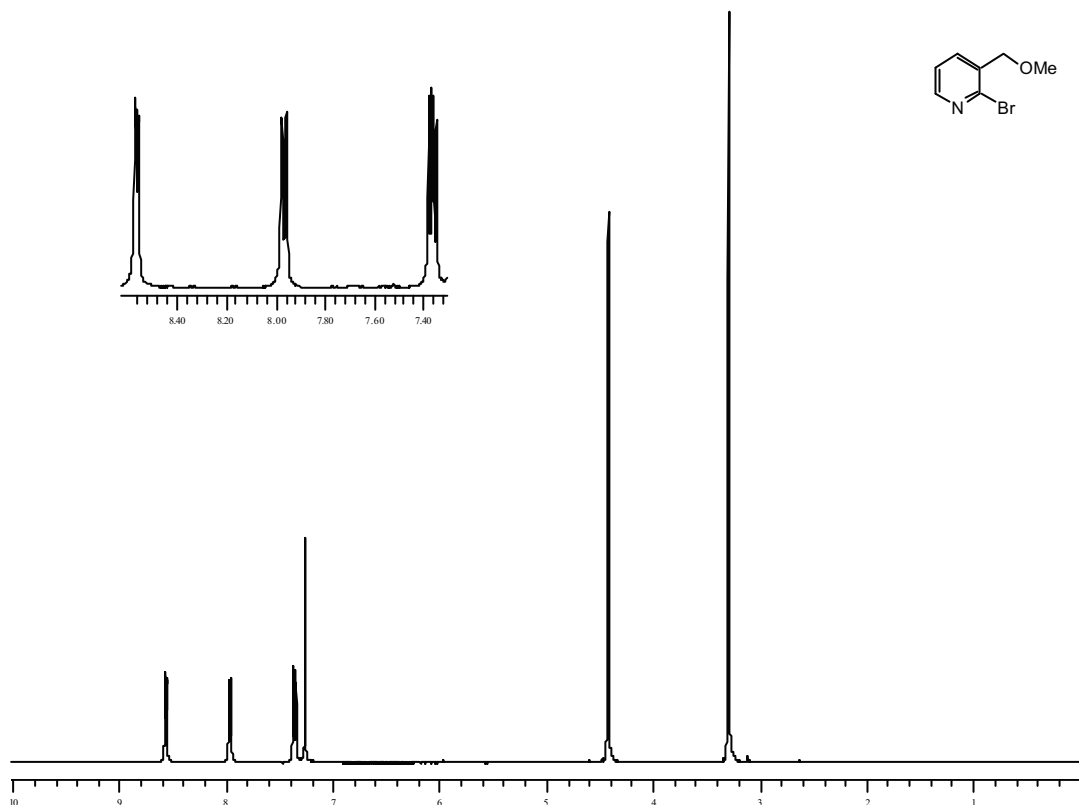
To a solution of *bromoacid* **140** (1.1 g, 5.4 mmol) and triethylamine (800 μL , 5.7 mmol) in benzene (80 mL) at room temperature was added ethyl chloroformate (540 μL , 5.7 mmol) and the resulting mixture stirred for 1 h at room temperature. The precipitated $\text{Et}_3\text{N}\cdot\text{HCl}$ was filtered off and the filtrate was evaporated to dryness to give the mixed anhydride as a colourless oil which was immediately dissolved in THF (20 mL) and added dropwise to a suspension of LiAlH_4 (0.22 g, 5.7 mmol) in THF (10 mL) at -78°C . The reaction mixture was stirred for 30 min at -78°C before the sequential addition of MeOH (20 mL) and a solution of aqueous NaOH (5 mL, 1N), and then warming to room temperature for 1.5 h. The reaction mixture was poured into H_2O (50 mL) and the resulting mixture was extracted in ethyl acetate (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO_4 and concentrated *in vacuo* to afford *alcohol* **144** (1.03 g, 94%) as a white amorphous solid. R_f 0.46 (hexane/ EtOAc , 1:1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3401, 2965, 1732, and 1600; δ_{H} (CDCl_3 , 400 MHz) 3.61 (1H, bs), 4.71 (2H, s), 7.25 (1H, dd, J 12.5 and 5.0 Hz) 7.83 (1H, bd, J 8.0 Hz) and 8.20 (1H, bd, J 6.0 Hz); δ_{C} (CDCl_3 , 100 MHz) 63.1 (t), 123.1 (d), 136.6 (d), 137.6 (s), 141.3 (s) and 148.4 (d); MS (CI^+) m/z 110 (100), 190 (MH^+ , 50), 205 (MH_4^+ , 10); HRMS (CI^+) calcd for $\text{C}_6\text{H}_7^{81}\text{BrNO}$ (MH^+) 189.9691, found 189.9685 ($\delta = -0.6$ ppm).

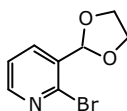
2-Bromo-3-methoxymethylpyridine (145)

C₇H₈BrNO
Exact Mass: 200.98
Mol. Wt.: 202.05

C, 41.61; H, 3.99; Br, 39.55; N, 6.93; O, 7.92

To a solution of *alcohol 144* (167 mg, 0.9 mmol) in THF (5 mL) at 0 °C was added NaH (38 mg, 1.0 mmol, 60% dispersion as mineral oil,) portionwise over a period of 5 min. The reaction mixture was stirred for 30 min and then a solution of methyl iodide (135 mg, 1.0 mmol) in THF (1 mL) was added dropwise. The resulting mixture was stirred for 30 min at room temperature, poured onto ice-water (10 mL) and extracted with benzene (3 × 50 mL). The combined organic extracts were washed with saturated aqueous NH₄Cl (50 mL) and brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (CHCl₃/Et₂O, 9:1) afforded *ether 145* (166 mg, 92%) as a colourless oil. *R_f* 0.25 (CHCl₃/Et₂O, 3:1); ν_{max} /cm⁻¹ (neat) 3425, 1697, 1637, 1574 and 1372; δ_{H} (CDCl₃, 400 MHz) 3.15 (3H, s), 4.41 (2H, s), 7.35 (1H, dd, *J* 12.5 and 5.0 Hz), 7.96 (1H, bd, *J* 8.0 Hz) and 8.58 (1H, bd, *J* 6.0 Hz); δ_{C} (CDCl₃, 100 MHz) 58.5 (q), 70.8 (t), 123.2 (d), 133.3 (s), 136.0 (d), 147.4 (d) and 155.5 (s); MS (CI⁺) *m/z* 202 (MH⁺, 100), 221 (20); HRMS (CI⁺) calcd for C₇H₉⁸¹BrNO (MH⁺) 203.9842, found 203.9847 (δ = + 0.5 ppm).



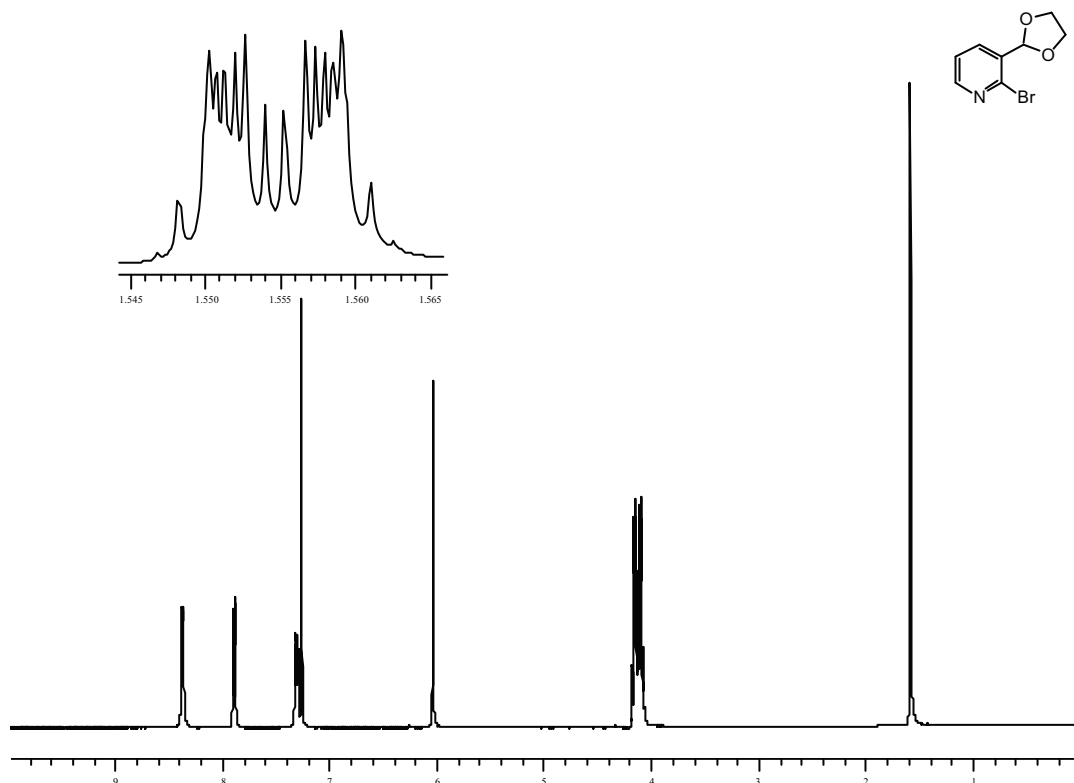
2-Bromo-3-[1,3]-dioxolan-2-ylpyridine (146)C₈H₈BrNO₂

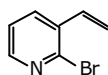
Exact Mass: 228.97

Mol. Wt.: 230.06

C, 41.77; H, 3.50; Br, 34.73; N, 6.09; O, 13.91

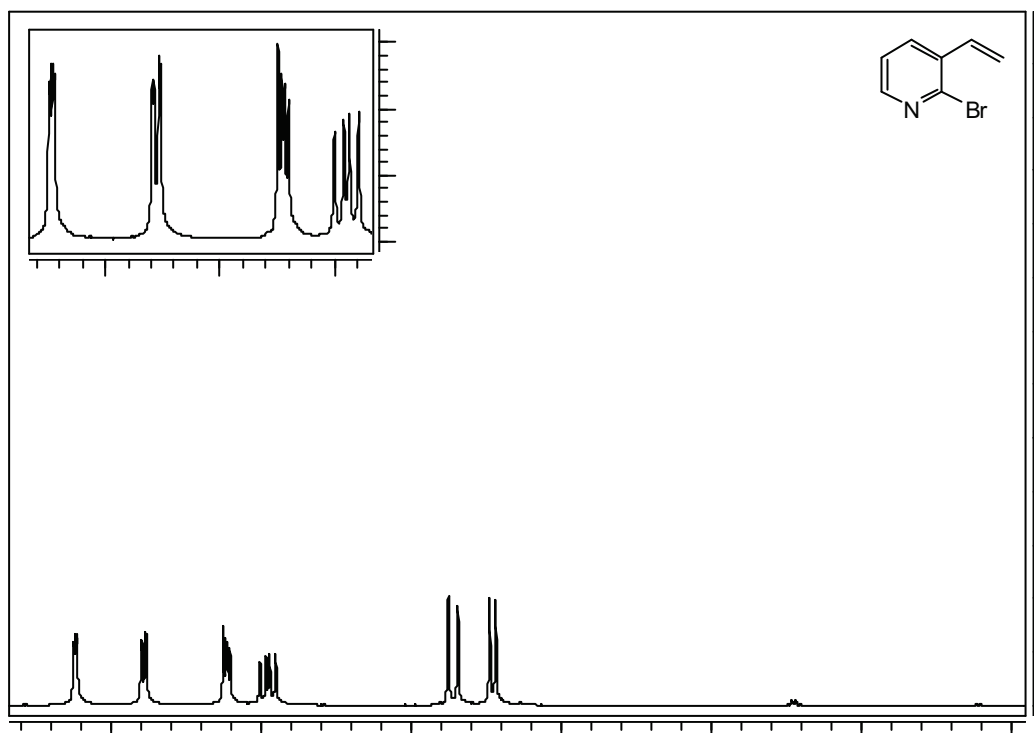
To a solution of *bromoaldehyde* **141** (100 mg, 0.5 mmol) in benzene (1 mL) was added ethylene glycol (66 μ L, 1.2 mmol) and pyridinium *para*-toluene sulfonate (298 mg, 1.2 mmol). The resultant suspension was stirred at room temperature for 14 h. The reaction mixture was concentrated *in vacuo* to give a pale yellow oil. Purification by FC (EtOAc/hexane, 1:9) afforded *dioxolane* **146** (69 mg, 60%) as an amorphous solid. *R_f* 0.43 (hexane/EtOAc, 1:1); ν_{max} /cm⁻¹ (neat) 1693, 1574, 1557, 1411, 1371, 1260 and 1052; δ_{H} (CDCl₃, 400 MHz) 4.06-4.18 (4H, CH₂), 6.04 (1H, s, CH), 7.31 (1H, m, NCHCH), 7.89 (1H, dd, *J* 6.0 and 2.0 Hz, NBrCCH) and 8.37 (1H, bd, *J* 3.0 Hz, NCH). δ_{C} (CDCl₃, 100 MHz) 65.6 (t), 101.7 (d), 122.8 (d), 134.2 (s), 136.4 (d), 142.5 (s), and 150.5 (d); MS (CI⁺) *m/z* 230 (MH⁺, 100), 247 (MNH₄⁺, 20), 152 (30), 102 (70); HRMS (CI⁺) calcd for C₈H₉⁷⁹BrNO₂ (MH⁺) 229.9817, found 229.9817 (δ = 0.0 ppm).

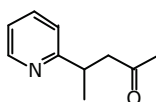


2-Bromo-3-vinylpyridine (147)

C₇H₆BrN
 Exact Mass: 182.97
 Mol. Wt.: 184.03
 C, 45.68; H, 3.29; Br, 43.42; N, 7.61

To an ice-cold suspension of methyl triphenylphosphonium bromide (433 mg, 1.2 mmol) in THF (10 mL) was added a solution of *n*-BuLi (2.2 M in hexanes, 548 μ L, 1.2 mmol) and the reaction mixture stirred at room temperature for 30 min. The solution was cooled to 0 °C, and a solution of *aldehyde* **141** (201 mg, 1.1 mmol) in THF (10 mL) was added dropwise. The reaction mixture allowed to warm to room temperature and stir for 14 h. The reaction mixture was quenched with H₂O (10 mL) and extracted with Et₂O (3 $\times$ 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (hexane/EtOAc, 9:1) afforded *vinylpyridine* **147** (192 mg, 87%) as a colourless oil. *R*_f 0.14 (hexane/EtOAc, 9:1); ν_{max} /cm⁻¹ (neat) 1628, 1573, 1378 and 1051; δ_{H} (CDCl₃, 270 MHz) 5.45 (1H, d, *J* 11.0 Hz, CH₂), 5.72 (1H, d, *J* 17.5 Hz, CH₂), 6.95 (1H, dd, *J* 17.5 and 11.0 Hz, CH), 7.23 (1H, m, NCHCH), 7.77 (1H, dd, *J* 7.5 and 1.5 Hz, BrCCCH) and 8.22 (1H, m, NCH). δ_{C} (CDCl₃, 100 MHz) 118.7 (t), 123.0 (d), 134.1 (d), 134.6 (d), 134.7 (s), 142.9 (s) and 148.9 (d); MS (CI⁺) *m/z* 186 (MH⁺, 100), 121 (100), 106 (100); HRMS (CI⁺) calcd for C₇H₇⁷⁹BrN (MH⁺) 185.9741, found 185.9745 (δ = + 0.4 ppm).



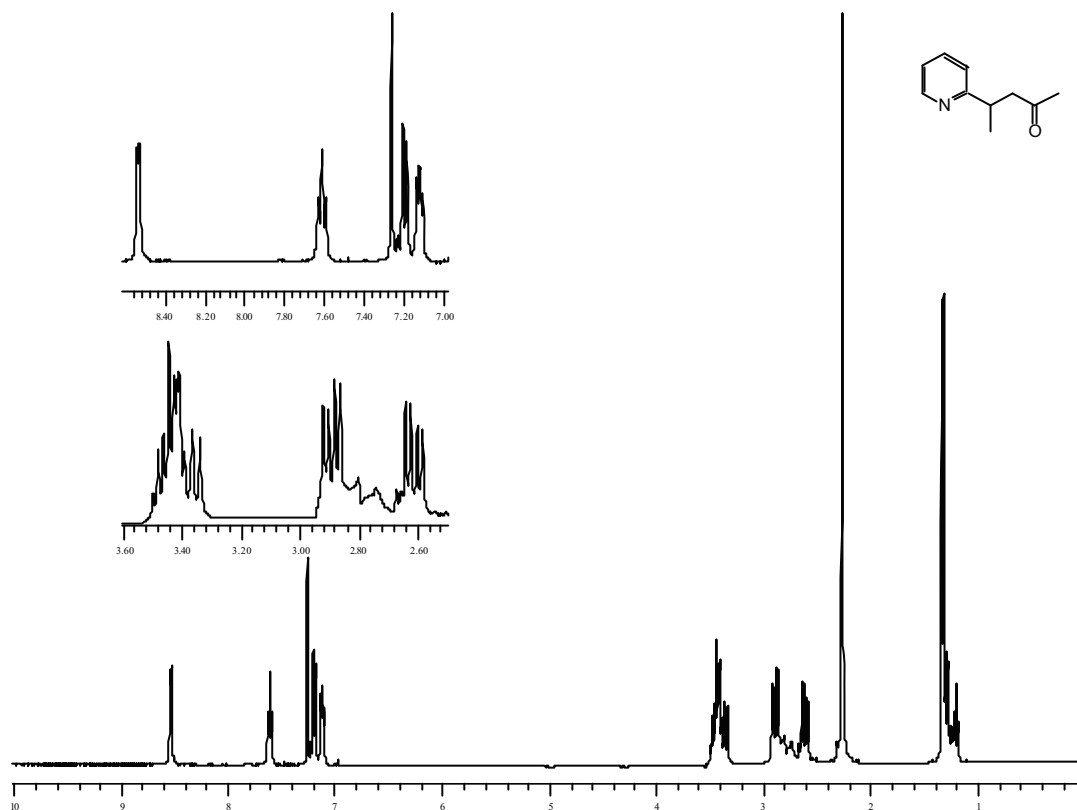
(±)-4-Pyridin-2'-yl pentan-2-one (148)

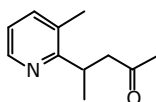
C₁₀H₁₃NO
 Exact Mass: 163.10
 Mol. Wt.: 163.22
 C, 73.59; H, 8.03; N, 8.58; O, 9.80

Method 1: To a solution of 2-bromopyridine (0.5 g, 3.2 mmol) in Et₂O (20 mL) at -78 °C was added a solution of BuLi (2.2 M in hexanes, 1.4 mL, 3.2 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (0.30 g, 1.6 mmol) in dibutylsulfide (600 µL, 3.2 mmol) and Et₂O (2.0 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of 3-penten-2-one (500 µL, 6.3 mmol). After stirring for 4 h at room temperature saturated aqueous ammonia (2 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 × 20 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 20 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (EtOAc/hexane, 1:9) afforded **ketone 148** (239 mg, 80%) as a colourless oil. *R*_f 0.24 (hexane/EtOAc, 1:1; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1579 (C=O), 1558, 1455 and 1418; δ_{H} (CDCl₃, 270 MHz) 1.22 (3H, d, *J* 7.0 Hz, CCHCH₃), 2.08 (3H, s, COCH₃), 2.65 (1H, dd, *J* 17.0 and 7.0 Hz, CH₂), 3.02 (1H, dd, *J* 17.0 and 7.0 Hz, CH₂), 3.40 (1H, m, PyCH), 7.05 (1H, ddd, *J* 1.5, 5.0 and 8.0 Hz, NCHCH), 7.15 (1H, bd, *J* 7.0 Hz, NCCH), 7.54 (1H, td, *J* 8.0 and 1.5 Hz, NCHCHCH) and 8.46 (1H, td, *J* 1.5 and 4.0 Hz NCH); δ_{C} (CDCl₃, 67.5 MHz) 21.1 (q), 30.6 (d), 37.0 (q), 49.7 (t), 121.4 (d), 122.3 (d), 136.5 (d), 149.2 (d), 164.8 (s) and 208.1 (s); MS (CI⁺) *m/z* 164 (MH⁺, 100), 147 (10), 94 (5); HRMS (CI⁺) calcd for C₁₀H₁₄NO (MH⁺) 164.1075, found 164.1070 (δ = - 0.5 ppm).

Method 2: To a solution of CuBr.SMe₂ (100 mg, 0.6 mmol) and 3-penten-2-one (59 µL, 0.6 mmol) in tBuOMe (1 mL) at -75 °C was added 2-pyridyl magnesium bromide (184 µL, 0.6 mmol) in Et₂O and the reaction mixture stirred for a 2 h. MeOH (500 µL) was added and the reaction mixture slowly warmed to room temperature. The reaction mixture was quenched with saturated aqueous NH₄Cl (500 µL). The resulting mixture was diluted with H₂O (500 µL) and extracted with Et₂O (3 × 500 µL). The combined organic extracts were washed with brine (2 mL), dried over MgSO₄ and concentrated *in vacuo* to give a colourless oil. Purification by FC (EtOAc/hexane, 1:9) afforded **ketone 148** (54 mg, 60%) as a

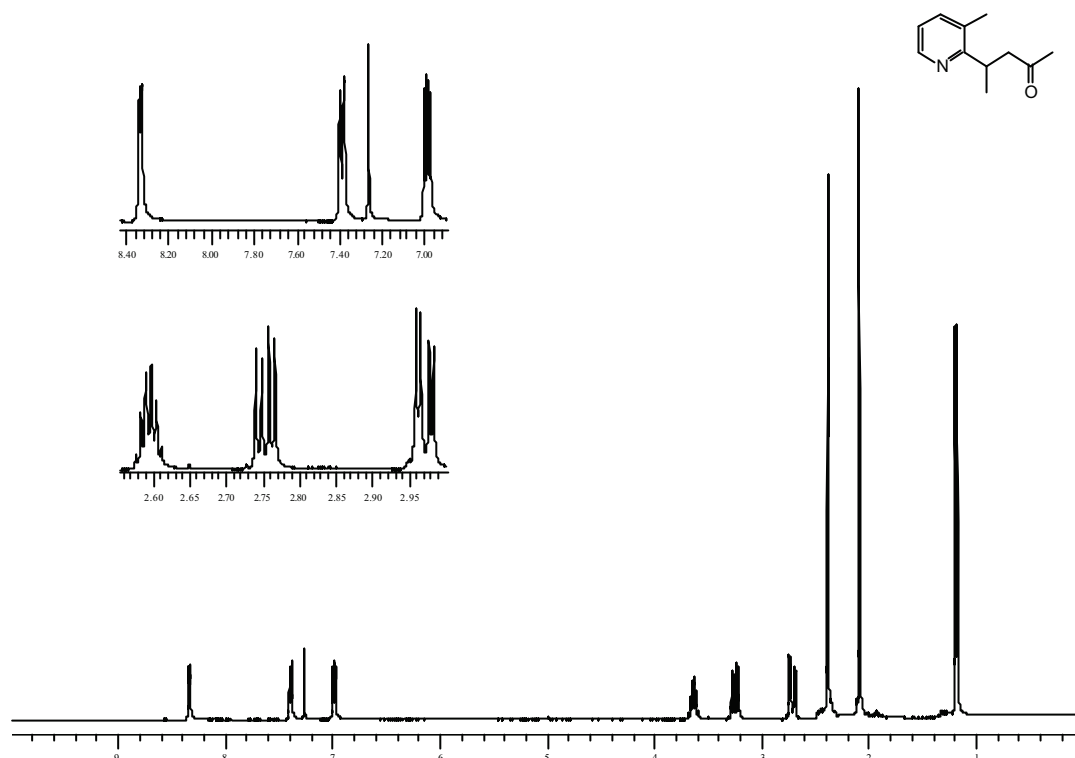
colourless oil. Chiralcel OD (0.46 cm $\times$ 25 cm) Hexane/*i*PrOH 95:5; 1 mL min⁻¹; 30 °C; UV detection at 220 nm, reference at 525 nm. Retention times: 7.5 min and 8.0 min. Spectroscopic data as above.



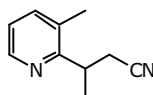
(±)-4-(3'-Methylpyridin-2'-yl) pentan-2-one (149)

C₁₁H₁₅NO
 Exact Mass: 177.12
 Mol. Wt.: 177.24
 C, 74.54; H, 8.53; N, 7.90; O, 9.03

To a solution of 2-bromo-3-methylpyridine (324 μ L, 2.8 mmol) in Et₂O (5 mL) at -78 °C was added a solution of BuLi (2.2 M in hexanes, 1.3 mL, 2.8 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (270 mg, 1.4 mmol) in dibutylsulfide (496 μ L, 2.8 mmol) and Et₂O (5.0 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of 3-penten-2-one (554 μ L, 5.7 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (2 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 $\times$ 20 mL). The organic extracts were combined and extracted with aqueous HCl (2 $\times$ 20 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 $\times$ 20 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (EtOAc/hexane, 1:9) afforded **ketone 149** (216 mg, 85%) as a colourless oil. *R*_f 0.60 (CHCl₃/Et₂O, 19:1); ν_{max} /cm⁻¹ (neat) 3445, 2964, 1708 (C=O), 1586, 1374, 1450, 1425 and 1356; δ_{H} (CDCl₃, 270 MHz) 1.17 (3H, d, *J* 7.0 Hz, CH₃CH), 2.07 (3H, s, ArCH₃), 2.37 (3H, s, COCH₃), 2.69 (1H, dd, *J* 17.5 and 8.0 Hz, CH₂), 3.23 (1H, dd, *J* 17.5 and 8.0 Hz, CH₂), 3.60 (1H, m, PyCH), 6.99 (1H, m, NCHCH), 7.37 (1H, d, *J* 7.5 Hz, NCHCHCH) and 8.32 (1H, d, *J* 5.0 Hz, NCH); δ_{C} (CDCl₃, 67.5 MHz) 18.8 (q), 20.4 (d), 30.7 (q), 32.1 (q), 49.3 (t), 121.1 (d), 130.6 (s), 137.9 (d), 146.6 (d), 163.3 (s) and 208.6 (s); MS (CI⁺) *m/z* 178 (MH⁺, 100), 147 (40), 94 (20); HRMS (CI⁺) calcd for C₁₁H₁₆NO (MH⁺) 178.1232, found 178.1228 (δ = - 0.4 ppm).



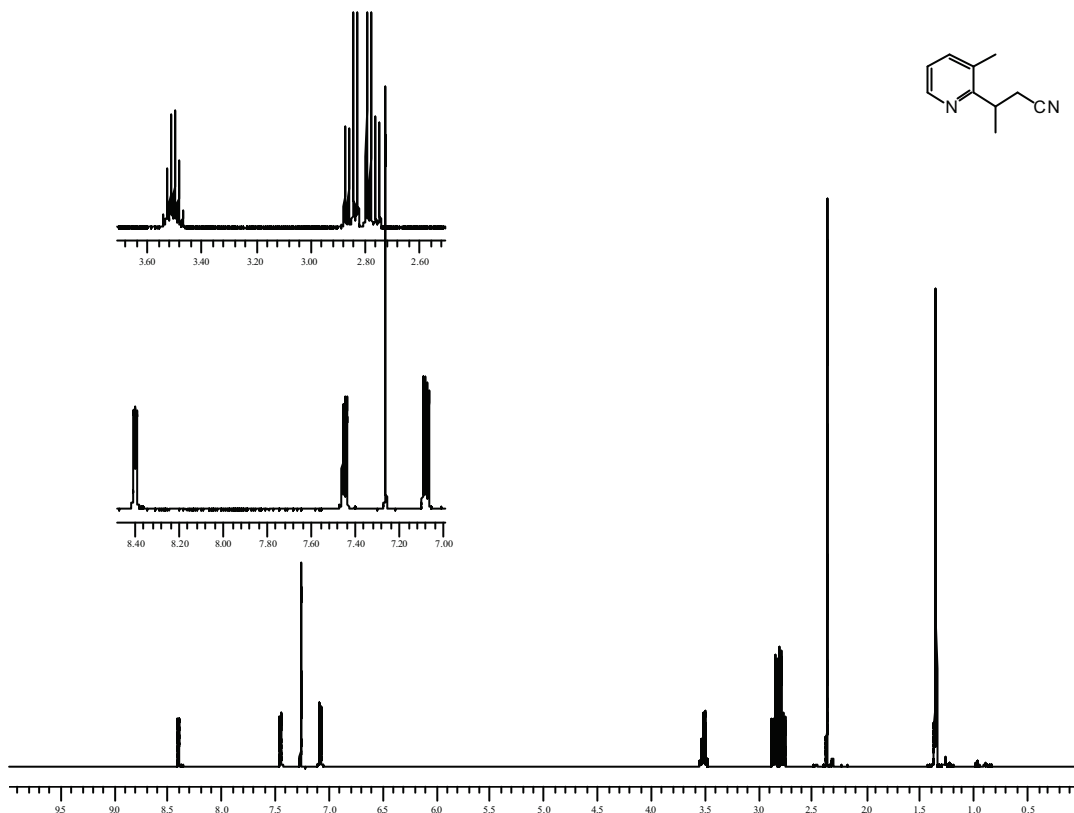
(±)-3-(3'-Methylpyridin-2'-yl) butyronitrile (150).



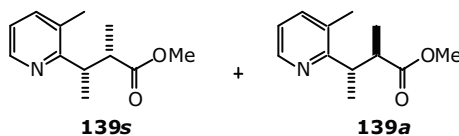
$C_{10}H_{12}N_2$
 Exact Mass: 160.10
 Mol. Wt.: 160.22
 C, 74.97; H, 7.55; N, 17.48

To a solution of *2-bromo-3-methylpyridine* (1.3 mL, 11.0 mmol) in Et_2O (20 mL) at $-78\text{ }^{\circ}C$ was added a solution of BuLi (2.3 M in hexanes, 5.0 mL, 11.0 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (1.14 g, 5.5 mmol) in dibutylsulfide (496 μL , 11.0 mmol) and Et_2O (20 mL) at $0\text{ }^{\circ}C$. The resulting dark solution was stirred for 15 min at room temperature before addition of 3-penten-2-one (896 μL , 11.0 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (2 mL) was added and the phases separated. The aqueous layer was extracted with Et_2O ($3 \times 20\text{ mL}$). The organic extracts were combined and extracted with aqueous HCl ($2 \times 20\text{ mL}$, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et_2O ($3 \times 20\text{ mL}$). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC ($EtOAc$ /hexane, 1:9) afforded *nitrile 150* (789 mg, 81%) as a colourless oil. R_f 0.23 (nHexane/ $EtOAc$, 90:10); ν_{max}/cm^{-1} (neat) 3424, 2972, 2934, 2874, 1638, 1582, 1451, 1426, 1375 and 1092; δ_H ($CDCl_3$, 500 MHz) 1.34 (3H, d, J 7.0 Hz, CH_3CH), 2.36 (3H, s, $ArCH_3$), 2.77 (1H, dd, J 17.0 and 7.0 Hz, CH_2), 2.87 (1H,

dd, J 17.0 and 7.0 Hz, CH_2), 3.48-3.52 (1H, m PyCH), 7.08 (1H, dd, J 4.5 and 7.5 Hz, NCHCH), 7.45 (1H, d, J 8.5 Hz, NCHCHCH) and 8.40 (1H, dd, J 1.5 and 4.5 Hz, NCH); δ_{C} (CDCl_3 , 125 MHz) 18.4 (q), 20.1 (q), 23.1 (t), 34.2 (d), 119.7 (s), 122.0 (d), 130.3 (s), 138.2 (d), 147.0 (d) and 159.8 (s); MS (CI^+) m/z 161 (MH^+ , 100) and 120 (15); HRMS (CI^+) calcd for $\text{C}_{11}\text{H}_{13}\text{N}_2$ (MH^+) 161.1079, found 161.1077 (Δ = - 1.1 ppm).



(±)-*syn*-2-Methyl-3-(3'-methylpyridin-2'-yl) butyric acid methyl ester (139s) and (±)-*anti*-2-methyl-3-(3'-methylpyridin-2'-yl) butyric acid methyl ester (139a)



$\text{C}_{12}\text{H}_{17}\text{NO}_2$
Exact Mass: 207.13
Mol. Wt.: 207.27
C, 69.54; H, 8.27; N, 6.76; O, 15.44

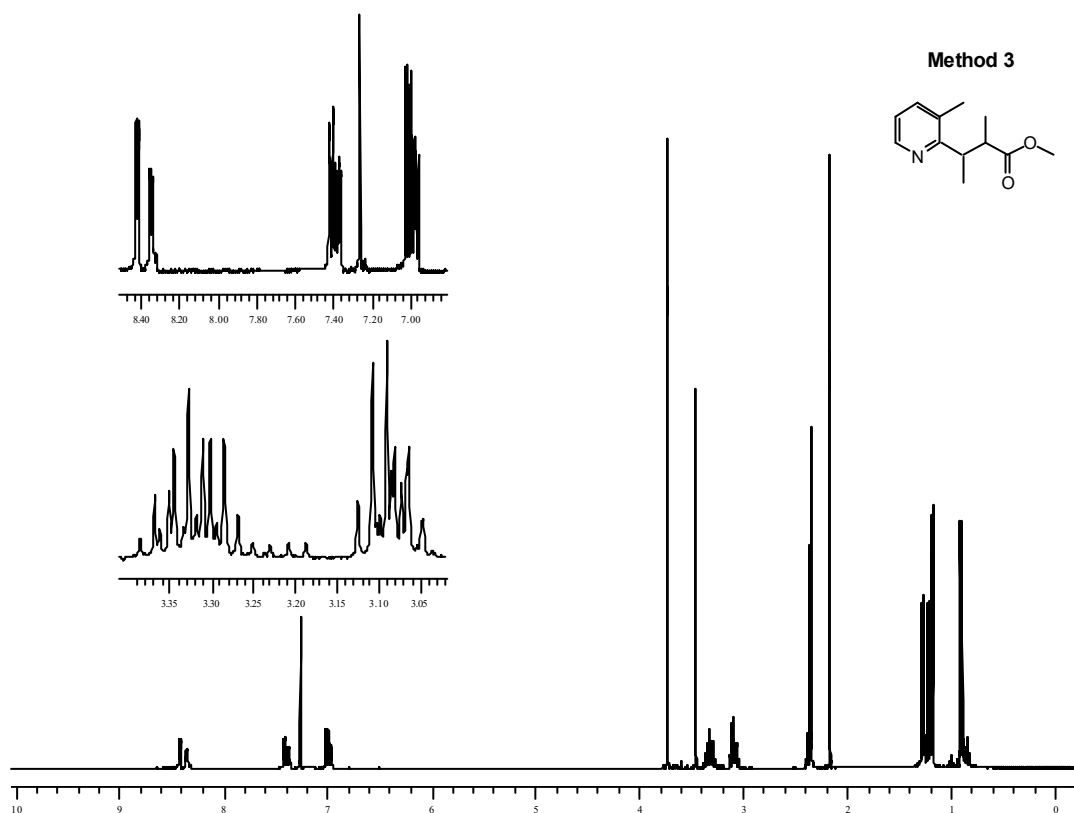
Method 1: To a solution of 2-bromo-3-methylpyridine (50 mg, 0.3 mmol) in Et_2O (10 mL) at -78°C was added a solution of BuLi (2.5 M in hexanes, 113 μL , 0.3 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (27 mg, 0.1 mmol) in dibutylsulfide (496 μL , 2.8 mmol) and Et_2O (15 mL) at 0°C . The resulting dark solution was

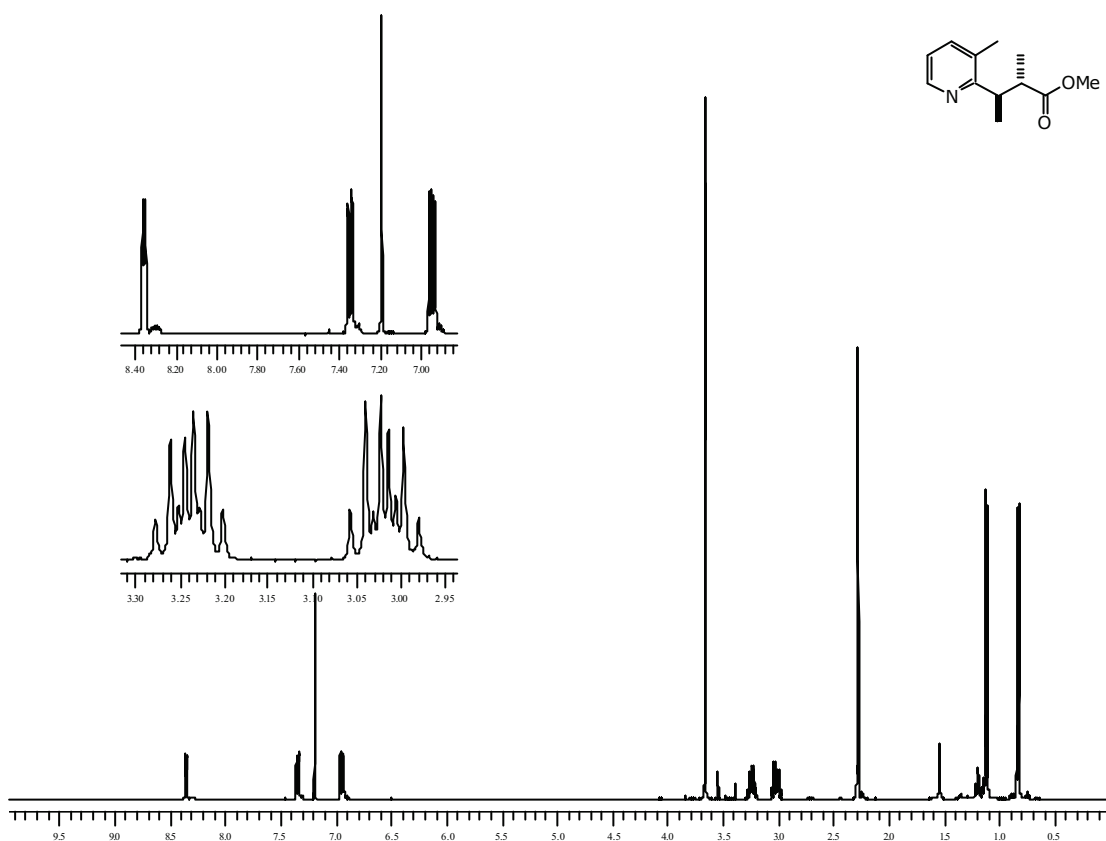
stirred for 15 min at room temperature before addition of methyl tiglate (39 mg, 0.3 mmol). After stirring for 24 h at room temperature saturated aqueous ammonia (5 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 × 20 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 20 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over MgSO₄ and concentrated *in vacuo* to give a colourless oil. Purification by FC (EtOAc/hexane, 1:9) afforded *esters* **139s** and **139a** (3 mg, 10%, *dr* 23:77, **139s**:**139a** by ¹H NMR) as a colourless oil. *R*_f 0.21 (hexane/EtOAc, 9:1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3433, 2973, 1733 (C=O), 1638, 1455 and 1164; δ_{H} (CDCl₃, 400 MHz) **139a**: 0.89 (3H, d, *J* 7.0 Hz, CH₃CHC), 1.19 (3H, d, *J* 7.0 Hz, CH₃CHCO), 2.19 (3H, s, ArCH₃), 3.05-3.12 (1H, m, CHCO₂CH₃), 3.26-3.40 (1H, PyCH), 3.72 (3H, s, OCH₃), 6.93-7.06 (1H, NCHCH), 7.40 (1H, d, *J* 7.0 Hz, NCHCHCH) and 8.41 (1H, bd, *J* 5.0 Hz, NCH); **139s**: 1.20 (3H, d, *J* 7.0 Hz, CH₃), 1.28 (3H, d, *J* 7.0 Hz, CH₃CHCO), 2.38 (3H, s, ArCH₃), 3.05-3.12 (1H, CHCO₂CH₃), 3.26-3.40 (1H, PyCH), 3.42 (3H, s, OCH₃), 6.93-7.06 (1H, NCHCH), 7.38 (1H, d, *J* 7.0 Hz, NCHCHCH) and 8.38 (1H, d, *J* 5.0 Hz, NCH); δ_{C} (CDCl₃, 100 MHz) **139a**: 16.6 (q), 19.4 (q), 19.7 (d), 40.3 (d), 45.4 (q), 51.9 (d), 121.4 (d), 131.5 (s), 138.1 (d), 147.5 (d), 162.0 (s) and 178.0 (s); **139s**: 16.0 (q), 18.0 (q), 19.6 (d), 40.0 (d), 44.9 (q), 51.9 (d), 121.4 (d), 130.0 (d), 138.1 (d), 147.0 (d), 163.1 (s) and 177.1 (s); MS (CI⁺) *m/z* 208 (MH⁺, 100), 121 (30), 85 (30); HRMS (CI⁺) calcd for C₁₂H₁₈NO₂ (MH⁺) 208.1338, found 208.1335 (δ = - 0.3 ppm).

Method 2: To a solution of 2-bromo-3-methylpyridine (50 mg, 0.3 mmol) in Et₂O (10 mL) at -78 °C was added a solution of BuLi (2.5 M in hexanes, 113 μ L, 0.3 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (27 mg, 0.1 mmol) in dibutylsulfide (496 μ L, 2.8 mmol) and Et₂O (15 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of methyl angelate (39 mg, 0.3 mmol). After stirring for 24 h at room temperature saturated aqueous ammonia (5 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 × 20 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 20 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with brine

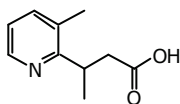
(30 mL, dried over MgSO_4 and concentrated *in vacuo* to give a colourless oil. Purification by FC (EtOAc/hexane, 1:9) afforded esters **139s** and **139a** (4 mg, 14%, *dr* 63:37, **139s**:**139a** by ^1H NMR) as a colourless oil. Spectroscopic data as above.

Method 3: A solution of LDA was prepared by the dropwise addition of a solution of *n*-BuLi (2.5 M in hexanes, 828 μL , 2.1 mmol) to a solution of *i*-Pr₂NH (290 μL , 2.1 mmol) in THF (2 mL) at -78°C followed by warming to 0°C for 1 h. This solution was cooled to -78°C and a solution of ester **138** (400 mg, 2.1 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at -78°C for 1 h, warmed to -50°C and a solution of MeI (129 μL , 2.1 mmol) in THF (10 μL) was added dropwise. The reaction mixture was allowed to warm to room temperature over a period of 1 h before addition of saturated aqueous NH_4Cl (1 mL). The resulting mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO_4 and concentrated *in vacuo* to give a colourless oil. Purification by FC (EtOAc/hexane, 1:9) afforded esters **139s** and **139a** (420 mg, 98%, *dr* 40:60, **139s**:**139a** by ^1H NMR) as a colourless oil. Spectroscopic data as above.



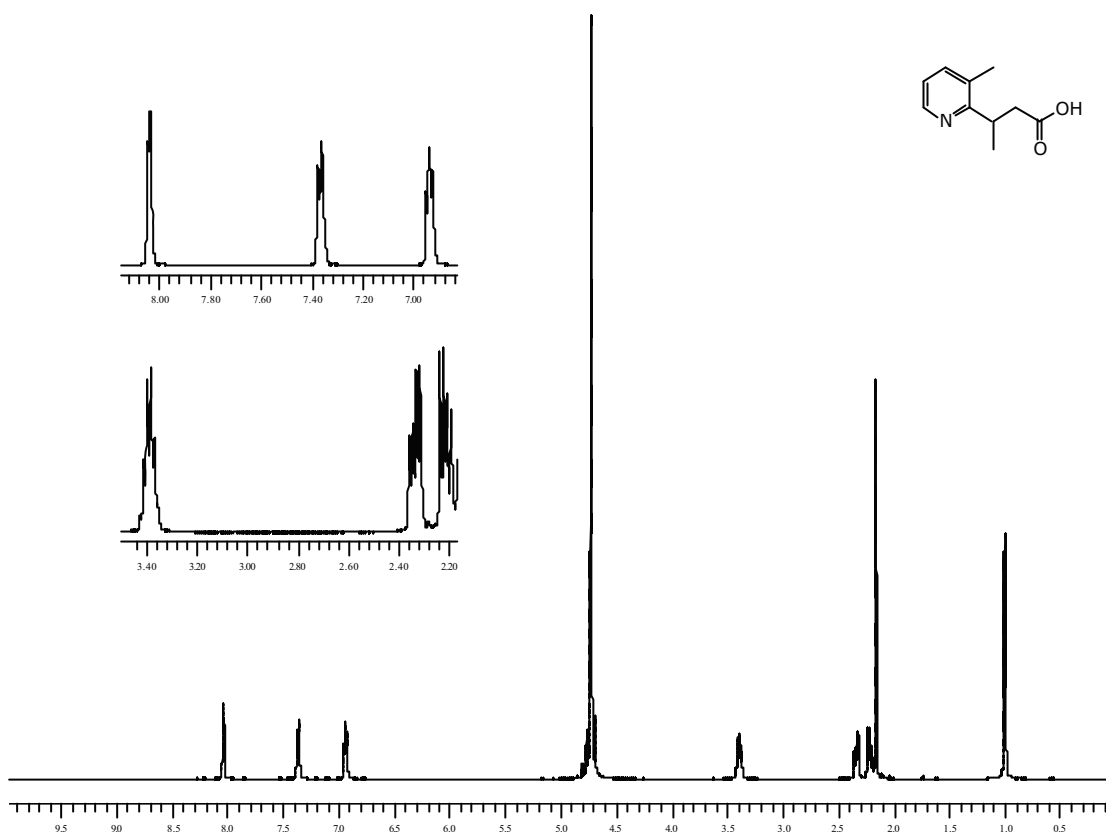


(±)-3-(3'-Methylpyridin-2'-yl) butyric acid (151)

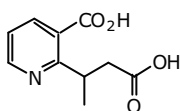


$C_{10}H_{13}NO_2$
 Exact Mass: 179.09
 Mol. Wt.: 179.22
 C, 67.02; H, 7.31; N, 7.82; O, 17.85

To a solution of ester **138** (50 mg, 0.3 mmol) in methanol (2 mL) was added NaOH (2M, 2 mL) and the resultant solution was heated to reflux for 14 h. The reaction mixture was neutralised with 2M HCl (ca. 2 mL) and concentrated *in vacuo* to afford a white hygroscopic solid. Purification by reverse C18 FC (CH_3CN) afforded acid **151** (46 mg, 86%) as a white hygroscopic solid. R_f 0.25 ($MeCN/H_2O$, 90:10); ν_{max}/cm^{-1} (neat) 1737 (C=O), 1574, 1443 and 1498; δ_H (d_6 -acetone, 270 MHz) 1.10 (3H, d, J 6.5 Hz, CH_3CH), 2.15 (1H, dd, J 8.0 and J 15.0 Hz, CH_2), 2.00 (1H, dd, J 8.0 and J 15.0 Hz, CH_2), 2.32 (3H, s, $ArCH_3$), 3.48 (1H, m, $PyCH$), 7.00 (1H, m, $NCHCH$), 7.42 (1H, d, J 7.5 Hz, $NCHCHCH$) and 8.27 (1H, d, J 4.0, NCH). δ_C (d_6 -acetone, 67.5 MHz) 18.92(q), 20.7(q), 34.9 (d), 45.7(t), 121.0(d), 130.4(s), 137.7(d), 146.6(d), 166.7(s) and 177.1(s); MS (CI^+) m/z 180 (MH^+ , 100), 179 (10), 178 (5), 90 (40); HRMS (CI^+) calcd for $C_{10}H_{13}NO_2^+$ 180.1025 (MH^+), found 180.1024 (MH^+) (δ = - 0.1 ppm).



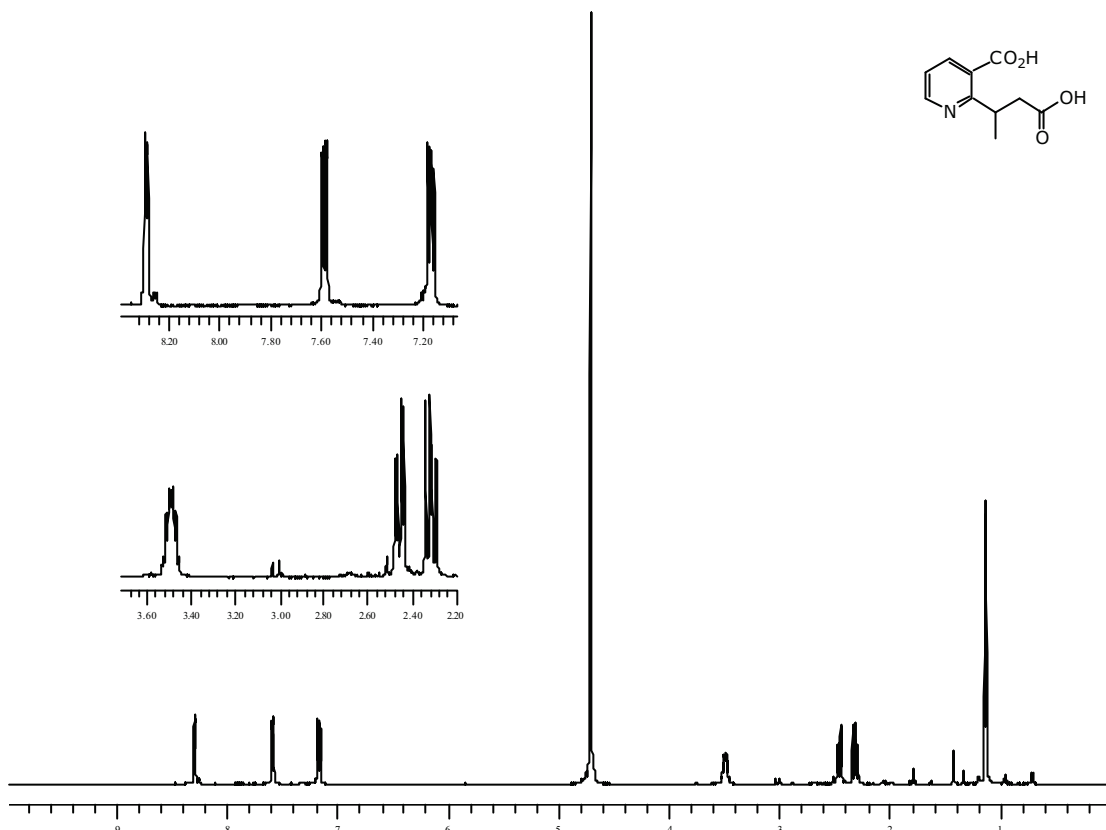
2-(2'-Carboxy-1'-methylethyl) nicotinic acid (**152**)



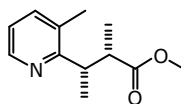
$C_{10}H_{11}NO_4$
 Exact Mass: 209.07
 Mol. Wt.: 209.20
 C, 57.41; H, 5.30; N, 6.70; O, 30.59

To a mixture of *nicotinic acid* **151** (100 mg, 0.6 mmol) and H_2O (500 μL) was added $KMnO_4$ (221 mg, 1.4 mmol) and heated to reflux overnight. After filtration of precipitated MnO_2 , the filtrate was concentrated to $\sim 200 \mu L$. The resulting clear solution was acidified to about pH3 with 1N HCl to give a precipitate, which was collected by filtration, dried *in vacuo* to reveal a amorphous solid. Purification by reverse phase C18 FC (CH_3CN) afforded *diacid* **152** (123 mg, 98%) as a white hygroscopic solid. R_f 0.12 (CH_3CN/H_2O , 5:1); ν_{max}/cm^{-1} (neat) 3449 (OH), 2958, 1736 (C=O), 1587, 1572, 1459, 1458, 1438 and 1194; δ_H (D_2O , 400 MHz) 1.13 (3H, d, J 7.0 Hz, $PyCHCH_3$), 2.30 (1H, dd, J 14 Hz, J 10 Hz, CH_2), 2.45 (1H, dd, J 14 and 10 Hz, CH_2), 3.46-3.51 (1H, m, $PyCH$), 7.15-7.18 (1H, dd, J 5.0 and 7.5 Hz, $NCHCH$), 7.57-7.59 (1H, dd, J 1.5 and 7.5 Hz, $NCHCHCH$) and 8.28-8.29 (1H, dd, J 1.5 and 5.0 Hz, NCH). δ_C (D_2O , 100 MHz) 19.5 (q), 35.6 (d), 44.1 (t), 122.2 (d), 136.0 (d), 148.0 (d), 159.7 (s), 168.4 (s), 177.0 (s) and 181.6 (s); MS (CI^+)

m/z 210 (MH^+ , 40), 91 (100), 74 (20) and 52 (40); HRMS (CI^+) calcd for $C_{11}H_{12}NO_4$ (MH^+) 210.0766, found 210.0766 ($\delta = -0.2$ ppm).



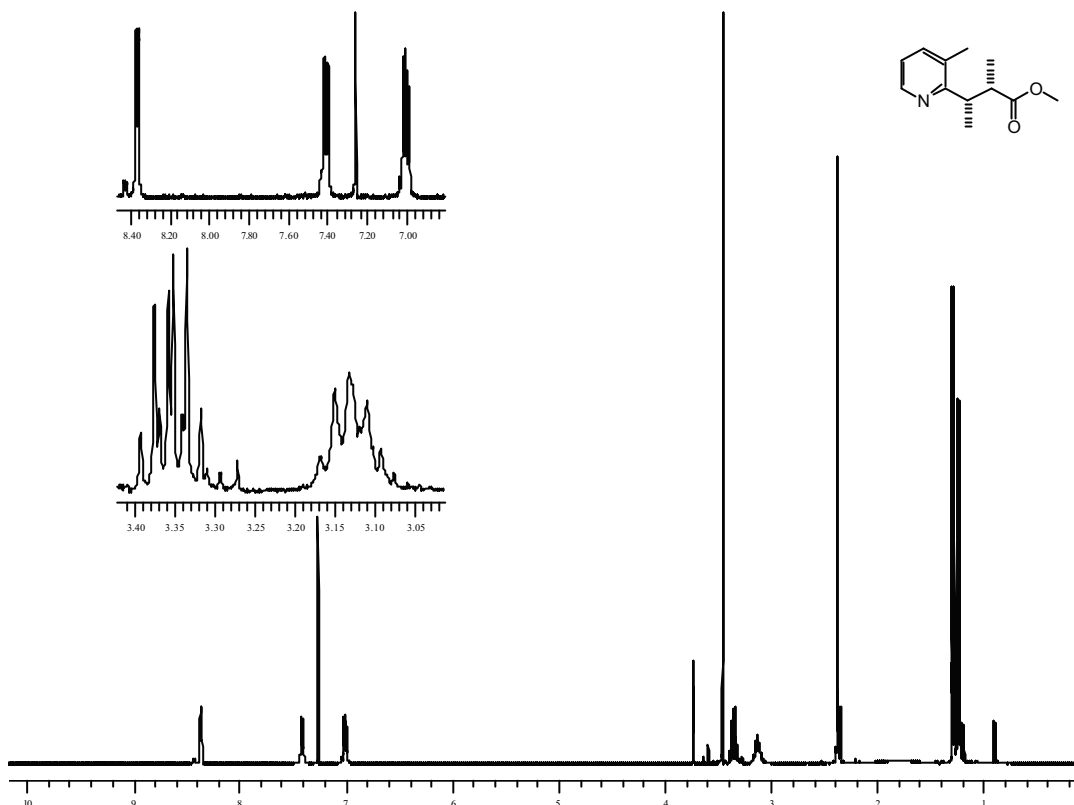
(±)-*syn*-2-Methyl-3-(3'-methylpyridin-2'-yl) butyric acid methyl ester (139s)



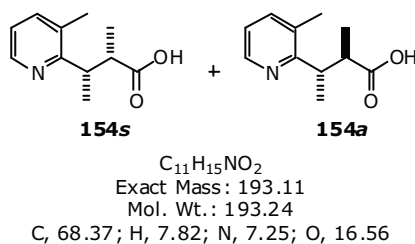
$C_{12}H_{17}NO_2$
Exact Mass: 207.13
Mol. Wt.: 207.27
C, 69.54; H, 8.27; N, 6.76; O, 15.44

To a solution of KHMDS (15% in toluene, 2.3 mL, 1.7 mmol) at -78 °C was added a solution of ester **138** (300 mg, 1.6 mmol) in toluene (2.0 mL). The reaction mixture was stirred at -78 °C for 1 h and then a solution of MeI (212 μ L, 2.4 mmol) in toluene (200 μ L) was added dropwise. The reaction mixture was left to stir for 36 h at -78 °C, after which time the reaction mixture was quenched with saturated aqueous NH_4Cl (1.0 mL). The resulting mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give ester **139s** (315 mg, 98%, *dr* 96:4, **139s**:**139a** by 1H NMR) as a colourless oil. R_f 0.21 (hexane/EtOAc, 90:10); ν_{max}/cm^{-1} (neat) 3429, 2966, 1733 ($C=O$), 1640, 1455 and 1165; δ_H ($CDCl_3$, 400 MHz) 1.11 (3H, d, J 7.0 Hz, CH_3CHC), 1.30 (3H, d, J 7.0 Hz, CH_3CHCO), 2.39 (3H, s, $ArCH_3$), 3.02-3.29 (1H, $CHCO_2CH_3$),

3.30-3.39 (1H, PyCH), 3.42 (3H, s, OCH₃), 7.01 (1H, m, NCHCH), 7.40 (1H, d, *J* 7.0 Hz, NCHCHCH) and 8.38 (1H, d, *J* 5.0 Hz, NCH); δ_c (CDCl₃, 100 MHz) 16.0 (q), 18.0 (q), 19.6 (d), 40.0 (d), 44.9 (q), 51.9 (d), 121.4 (d) 130.0 (d), 138.1 (d), 147.0 (d), 163.1 (s) and 177.1 (s); MS (CI⁺) *m/z* 208 (MH⁺, 80), 194 (100); HRMS (CI⁺) calcd for C₁₂H₁₈NO₂ (MH⁺) 208.1338, found 208.1342 (? = + 2.1 ppm).

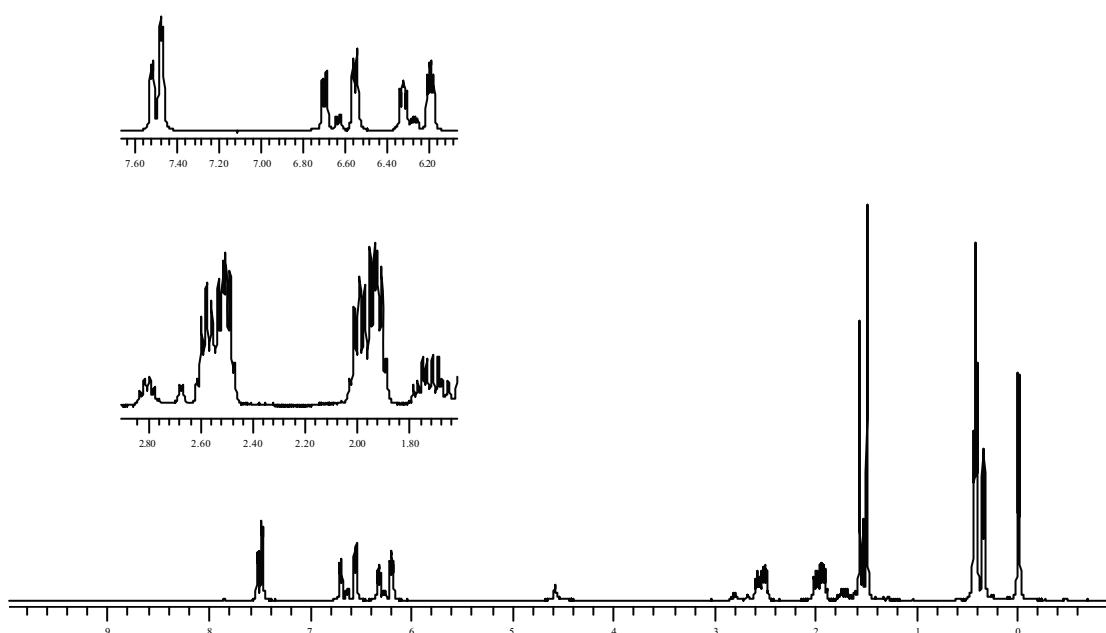
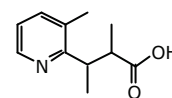


(±)-*syn*-2-Methyl-3-(3'-methylpyridin-2'-yl) butyric acid (154s) and (±)-*anti*-2-methyl-3-(3'-methylpyridin-2'-yl) butyric acid (154a)

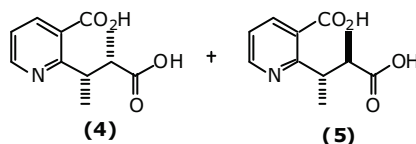


To a mixture of esters **139** (*dr* 40:60 **139s**:**139a**) (50 mg, 0.2 mmol) in methanol (1 mL) was added 2M NaOH (1 mL) and the resultant solution was heated to reflux for 14 h. The reaction mixture was neutralised with 2M HCl (*ca.* 1 mL) and concentrated in *vacuo* to give a white hygroscopic solid. Purification by reverse C18 FC (CH₃CN) afforded acids **154s** and **154a** (43 mg, 92%, *dr* 40:60, **154s**:**154a** by ¹H NMR) as a white hygroscopic solid. *R_f* 0.53 (CH₃CN/H₂O, 9:1); $\nu_{\max}$ /cm⁻¹ (neat) 3419, 2528, 1645 (C=O) and 1438; **154a**: δ_H (D₂O, 400 MHz)

0.50 (3H, d, J 14.0 Hz, NCCHCH₃), 0.81-1.01 (3H, d, J 14.0 Hz, COOHCHCH₃), 2.06 (3H, s, ArCH₃), 2.31-2.52 (1H, m, CHCOOH), 2.93-3.15 (1H, m, PyCH), 6.75-6.90 (1H, m, NCHCH), 7.15-7.81 (1H, m, NCHCHCH) and 8.00 (1H, bs, NCH). **154s**: δ_{H} (CDCl₃, 400 MHz) 0.80-1.01 (6H, m, COOHCHCH₃, NCHCH₃), 2.09 (3H, s, ArCH₃), 2.31-2.52 (1H, m, CHCOOH), 2.93-3.15 (1H, m, PyCH), 6.75-6.90 (1H, m, NCHCH), 7.15-7.81 (1H, m, NCHCHCH) and 8.00 (1H, bs, NCH). **154a**: δ_{C} (CDCl₃, 100 MHz) 16.1(q), 19.2(q), 44.7(d), 45.3(d), 51.4(q), 121.6(d), 122.9(d), 136.5(d), 149.3(d), 163.4(s) and 176.7(s); **154s**: δ_{C} (CDCl₃, 100 MHz) 15.4(q), 16.1(q), 18.1(q), 39.2(d), 47.9(d), 121.5(d), 131.6(s), 139.0(d), 145.5(d), 163.4(s), and 185.39(s); MS (CI⁺) m/z 194 (MH⁺, 100), 180 (40), 90 (10); HRMS (CI⁺) calcd for C₁₁H₁₅NO₂⁺ 194.1181 (MH⁺), found 194.1182 (MH⁺) (? = + 0.1 ppm).



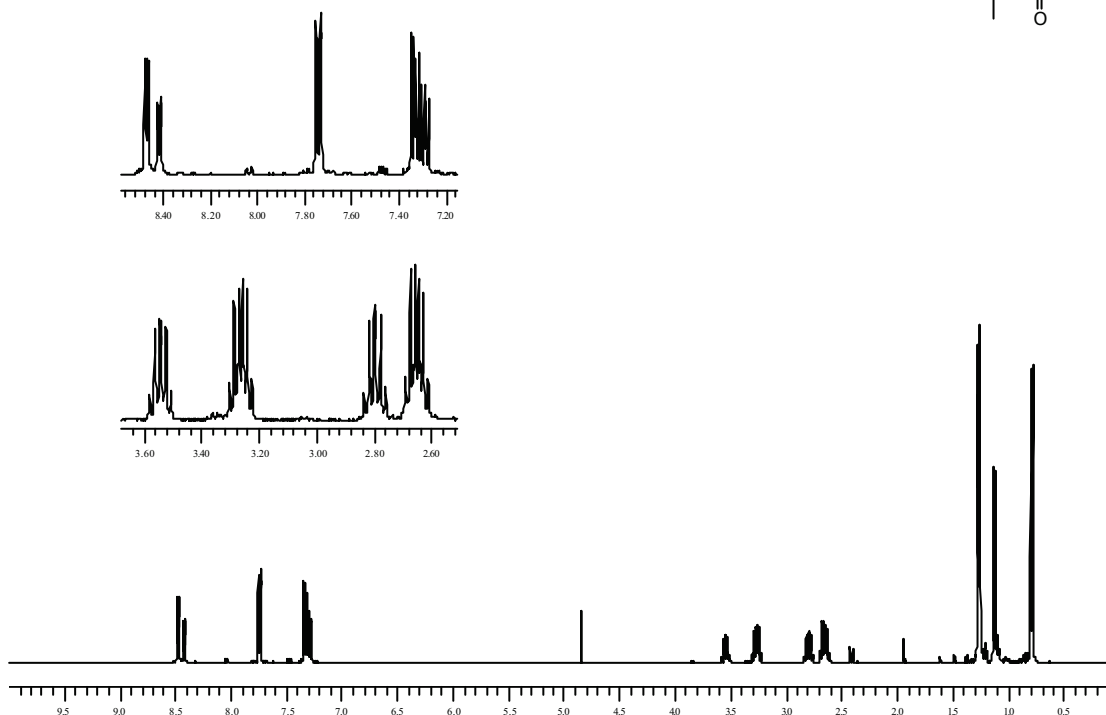
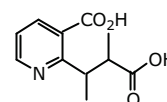
(±)-Evoninic acid (4) and (±)-*epi*-evoninic acid (5)

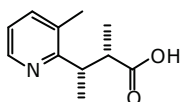


C₁₁H₁₃NO₄
 Exact Mass: 223.08
 Mol. Wt.: 223.23
 C, 59.19; H, 5.87; N, 6.27; O, 28.67

To a mixture of *butyric acid* **154** (*dr* 40:60, **154s**:**154a**) (50 mg, 0.3 mmol) and H₂O (1 mL) was added KMnO₄ (102 mg, 0.7 mmol) and heated to reflux overnight. After filtration of precipitated MnO₂, the filtrate was concentrated to

approx. 200 μL . The resulting clear solution was acidified to about pH3 with 1N HCl. Purification by reverse phase C18 FC (CH_3CN) afforded *diacids* **(4)** and **(5)** [65 mg, 98%, *dr* 40:60, **(4)**:**(5)** by ^1H NMR] as a white hygroscopic solid. *R_f* 0.09 ($\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 90:10); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3436, 3055, 2976, 2878, 1729, 1648 ($\text{C}=\text{O}$), 1587, 1452 and 1196; **(5)**: δ_{H} (D_2O , 400 MHz) 0.80 (3H, d, *J* 16.0 Hz, NCCHCH_3), 1.27 (3H, d, *J* 12.0 Hz, COOHCHCH_3), 2.62-2.71 (1H, m, PyCH), 3.24-3.32 (1H, m, CHCOOH), 7.26-7.37 (1H, dd, *J* 8.0 and 6.5 Hz, NCHCH), 7.75 (1H, d, *J* 8.0 Hz, NCHCHCH) and 8.48 (1H, d, *J* 6.5 Hz, NCH). **(4)**: δ_{H} (D_2O , 400 MHz) (3H, d, *J* 16.0 Hz, PyCHCH_3), 1.27 (3H, d, *J* 12.0 Hz, COOHCHCH_3), 2.75-2.85 (1H, m, CHCOOH), 3.51-3.60 (1H, m, PyCH), 7.26-7.37 (1H, dd, *J* 5.0 and 8.0 Hz, NCHCH), 7.75 (1H, d, *J* 8.0 Hz NCHCHCH) and 8.42 (1H, d, *J* 6.5 Hz, NCH). δ_{C} (D_2O , 100 MHz) 16.9 (q), 19.5 (q), 41.2 (d), 42.1 (d), 48.0 (d), 49.5 (q), 121.8 (d), 122.0 (d), 135.1 (d), 135.6 (s), 135.8 (d), 137.0 (s), 148.1 (d), 148.5 (d), 159.0 (s), 160.9 (s), 177.3 (s), 177.3 (s) and 185.9 (s); MS (CI^+) *m/z* 224 (MH^+ , 100), 101 (10), 20 (30); HRMS (CI^+) calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_4$ (MH^+) 224.3232, found 224.3235 ($\delta = + 0.3$ ppm).

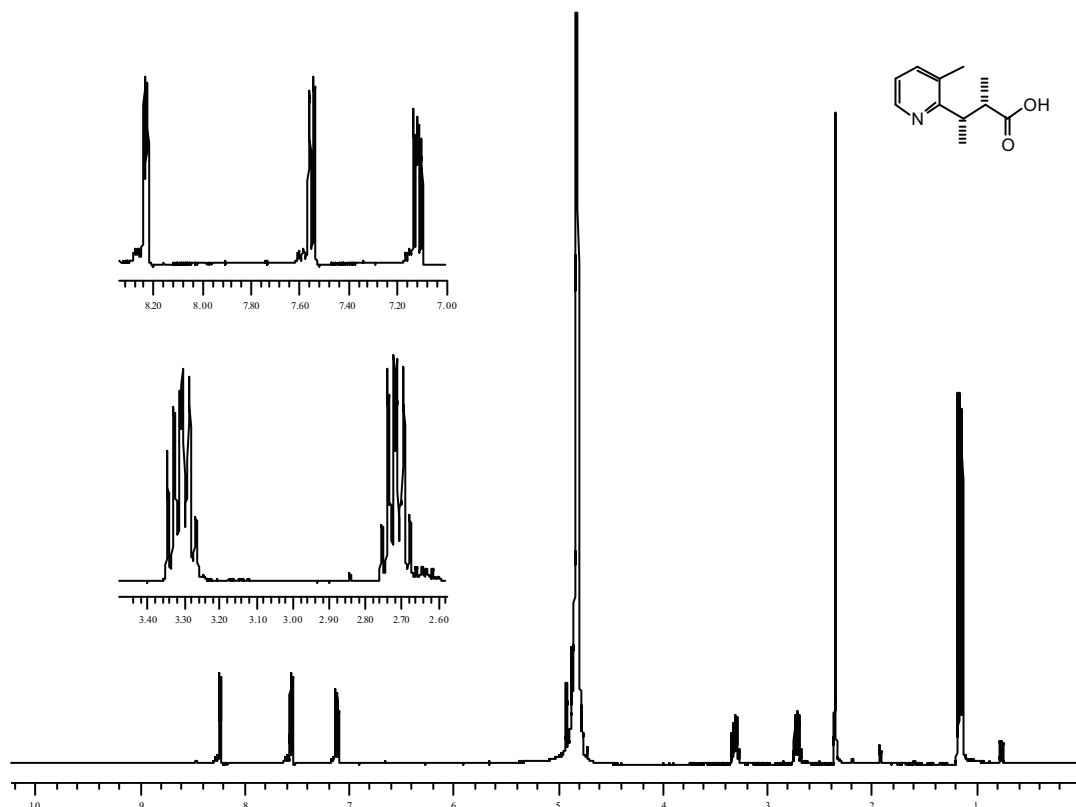


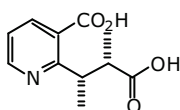
(±)-*syn*-2-Methyl-3-(3-methylpyridin-2-yl) butyric acid (154s**)**

C₁₁H₁₅NO₂
Exact Mass: 193.11
Mol. Wt.: 193.24

C, 68.37; H, 7.82; N, 7.25; O, 16.56

To a solution of ester **139s** (*dr* 96:4, **139s**:**139a**) (50 mg, 0.2 mmol) in methanol (1 mL) was added aqueous NaOH (1 mL, 2 M) and the resulting solution was heated at reflux for 14 h. The reaction mixture was neutralised with aqueous HCl (~1.0 mL, 2 M) and concentrated in *vacuo* to give a white hygroscopic solid. Purification by reverse phase C18 FC (CH₃CN) afforded acid **154s** (37 mg, 96%, *dr* 97:3, **154s**:**154a** by ¹H NMR) a white hygroscopic solid. *R*_f 0.53 (CH₃CN/H₂O, 90:10); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3449, 2098, 1639 (C=O), 1551, 1457, 1409 and 1367; δ_{H} (CDCl₃, 400 MHz) 1.14 (3H, d, *J* 8.0 Hz, ArCH₃), 1.17 (3H, d, *J* 8.0 Hz, COOHCHCH₃), 2.35 (3H, s, ArCH₃), 2.68-2.76 (1H, CHCOOH), 3.27-3.35 (1H, m, PyCH), 7.10-7.13 (1H, NCHCH), 7.54 (1H, bd, *J* 8.0 Hz, NCHCHCH) and 8.22 (1H, bd, *J* 5.0 Hz, NCH); δ_{C} (CDCl₃, 100 MHz) 15.4 (q), 16.1 (q), 18.1 (q), 39.2 (d), 47.9 (d), 121.5 (d), 131.6 (s), 139.0 (d), 145.5 (d), 163.4 (s), and 185.4 (s); MS (CI⁺) *m/z* 194 (MH⁺, 100), 186 (40), 73 (40); HRMS (CI⁺) calcd for C₁₁H₁₆NO₂ (MH⁺) 194.1167, found 194.1173 (Δ = + 0.6 ppm).

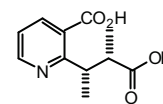
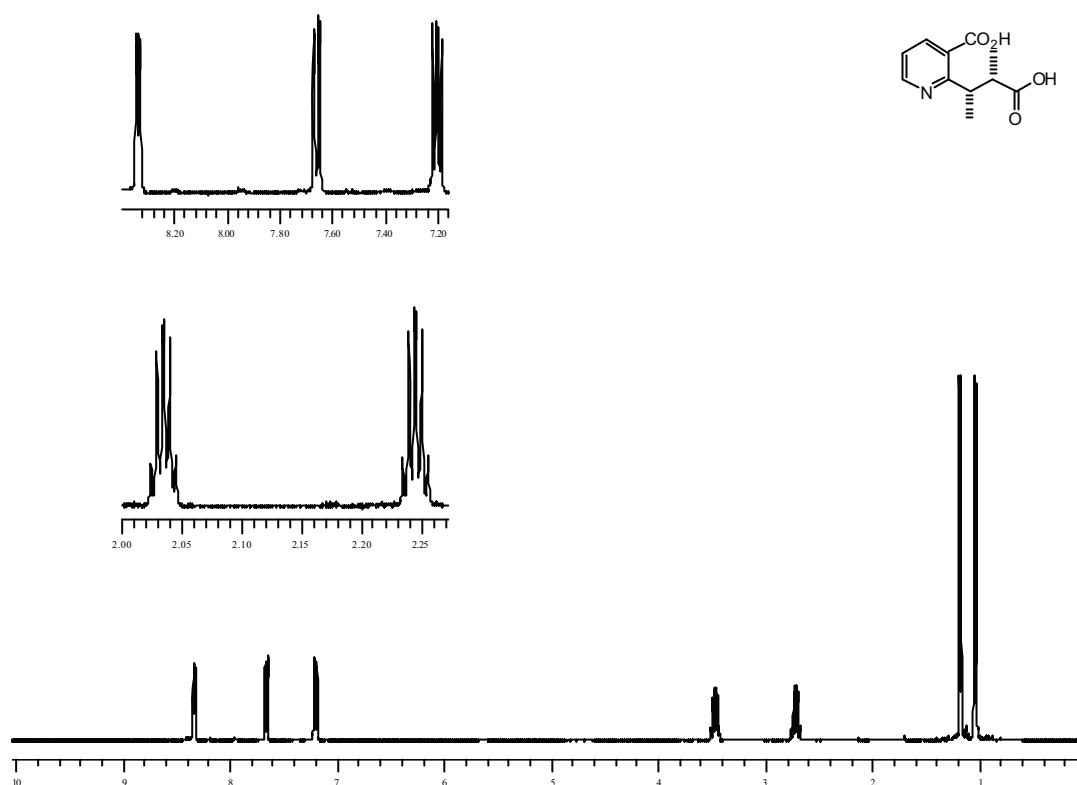


(±)-Evoninic acid (4)²²

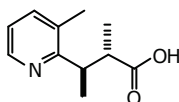
C₁₁H₁₃NO₄
Exact Mass: 223.08
Mol. Wt.: 223.23

C, 59.19; H, 5.87; N, 6.27; O, 28.67

To a solution of *acid 154s* (*dr* 97:3, **154s:154s**) (50 mg, 0.3 mmol) in H₂O (1 mL) at room temperature was added KMnO₄ (102 mg, 0.7 mmol) and the resulting solution was heated at reflux for 14 h. The reaction mixture was filtered and the filtrate was concentrated to ~200 µL. This clear solution was neutralised to pH 7 with aqueous HCl (1 M) to give a white hygroscopic solid. Purification by reverse phase C18 FC (CH₃CN) afforded *evoninic acid (4)* (65 mg, 98%, *dr* 98:2, **(4):(5)** by ¹H NMR) as a white hygroscopic solid. Recrystallisation (petroleum ether) gave pure *evoninic acid (4)* (37 mg, 55%). mp 134–137 °C (*cf.* lit.²² 132–136 °C); *R_f* 0.09 (CH₃CN/H₂O, 90:10); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3442, 2519, 2381, 2088, 1645 (C=O), 1436 and 1238; δ_{H} (D₂O, 400 MHz) 1.04 (3H, d, *J* 7.0 Hz, PyCHCH₃), 1.17 (3H, d, *J* 7.0 Hz, COOHCHCH₃), 2.68–2.76 (1H, m, CHCOOH), 3.43–3.51 (1H, m, PyCH), 7.20 (1H, dd, *J* 8.0 and 5.0 Hz, NCHCH), 7.65 (1H, dd, *J* 8.0 and 1.5 Hz, NCHCHCH) and 8.33 (1H, dd, *J* 5.0 and 1.5 Hz, NCH); δ_{C} (D₂O, 100 MHz) 14.8 (q), 16.5 (q), 40.9 (d), 47.6 (d), 121.4 (d), 135.2 (s), 135.4 (d), 160.6 (d), 160.6 (s), 176.9 (s) and 185.0 (s); MS (CI⁺) *m/z* 224 (MH⁺, 10), 233 (100); HRMS (CI⁺) calcd for C₁₁H₁₄NO₄ (MH⁺) 223.0845, found 223.0845 (δ = + 0.0 ppm).



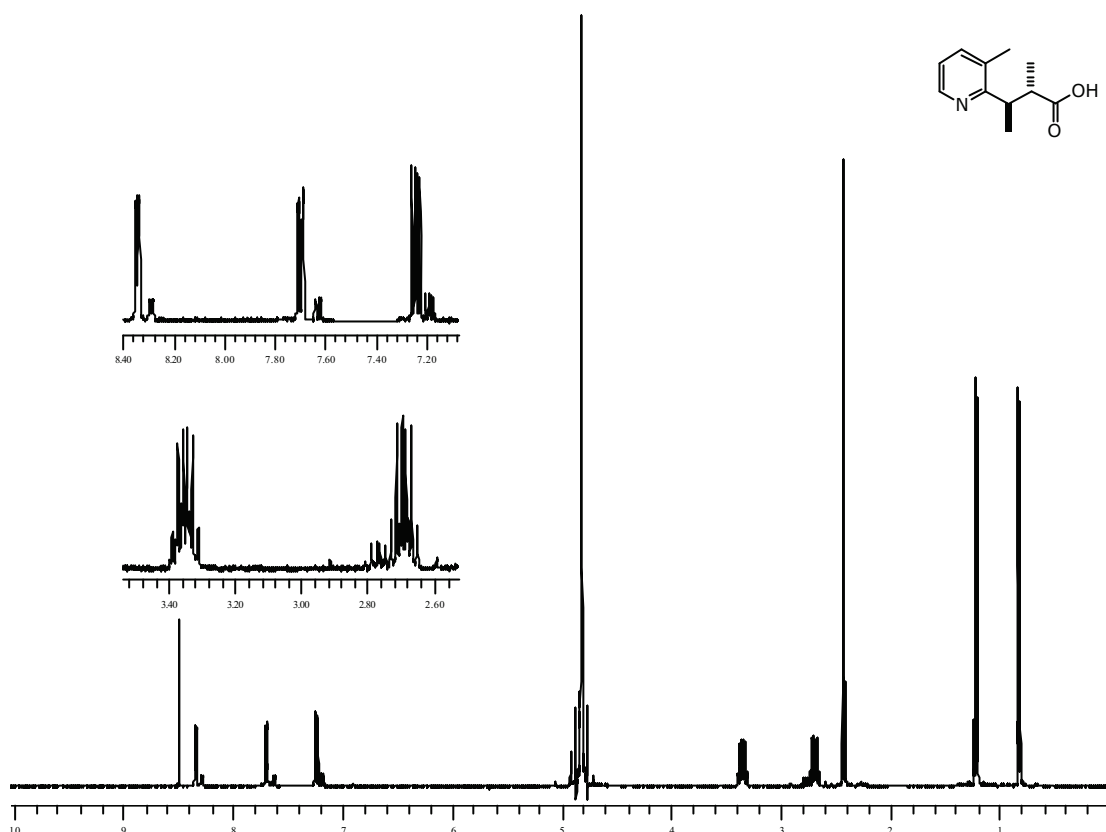
(±)-*anti*-2-Methyl-3-(3'-methylpyridin-2'-yl) butyric acid (154a)



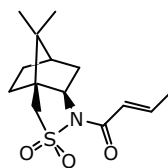
$C_{11}H_{15}NO_2$
Exact Mass: 193.11
Mol. Wt.: 193.24

C, 68.37; H, 7.82; N, 7.25; O, 16.56

To a solution of ester **139a** [*dr* >99:1 **139a**:**139s** (from repeated FC on the mix of esters obtained from **method 3: pp 162**)] (50 mg, 0.2 mmol) in methanol (1 mL) was added 2M NaOH (1 mL) and the resultant solution was heated to reflux for 14 h. The reaction mixture was neutralised with 2M HCl (*ca.* 1 mL) and concentrated in *vacuo* to give a white hygroscopic solid. Purification by reverse phase C18 FC (CH_3CN) afforded acid **154a** (45 mg, 97%, *dr* 40:60 **154a**:**154s** by 1H NMR) as a white hygroscopic solid. R_f 0.54 (CH_3CN/H_2O , 90:10); ν_{max}/cm^{-1} (neat) 3419, 2528, 1645 (C=O) and 1438; δ_H (D_2O , 400 MHz) 0.82 (3H, d, J 14.0 Hz, $NCCHCH_3$), 1.21 (3H, d, J 7.0 Hz, $COOHCHCH_3$), 2.43 (3H, s, $ArCH_3$), 2.65–2.73 (1H, m, CH), 3.31–3.39 (1H, m, PyCH), 7.24 (1H, dd, J 5.0 and 8.0 Hz, $NCHCH$), 7.69 (1H, bd, J 5.0 Hz, $NCHCHCH$) and 8.34 (1H, bd, J 5.0 Hz, NCH). δ_C ($CDCl_3$, 100 MHz) 16.1 (q), 19.2 (q), 44.7 (d), 45.3 (d), 51.4 (q), 121.6 (d), 122.9 (d), 136.5 (d), 149.3 (d), 163.4 (s) and 176.7 (s); MS (CI^+) m/z 194 (MH^+ , 10), 100 (20). HRMS (CI^+) calcd for $C_{11}H_{15}NO_2^+$ 194.1181 (MH^+), found 194.1182 (MH^+) ($? = + 0.1$ ppm).



(2R)-N-[(E)-2-Butenoyl] bornane-10,2-sultam (156)¹⁰⁷



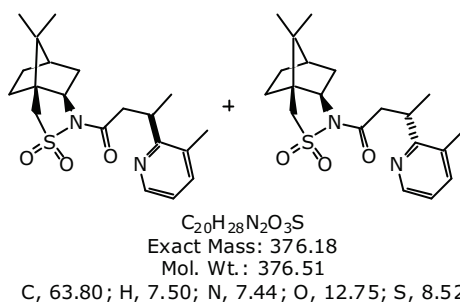
C₁₄H₂₁NO₃S
Exact Mass: 283.12
Mol. Wt.: 283.39

C, 59.34; H, 7.47; N, 4.94; O, 16.94; S, 11.32

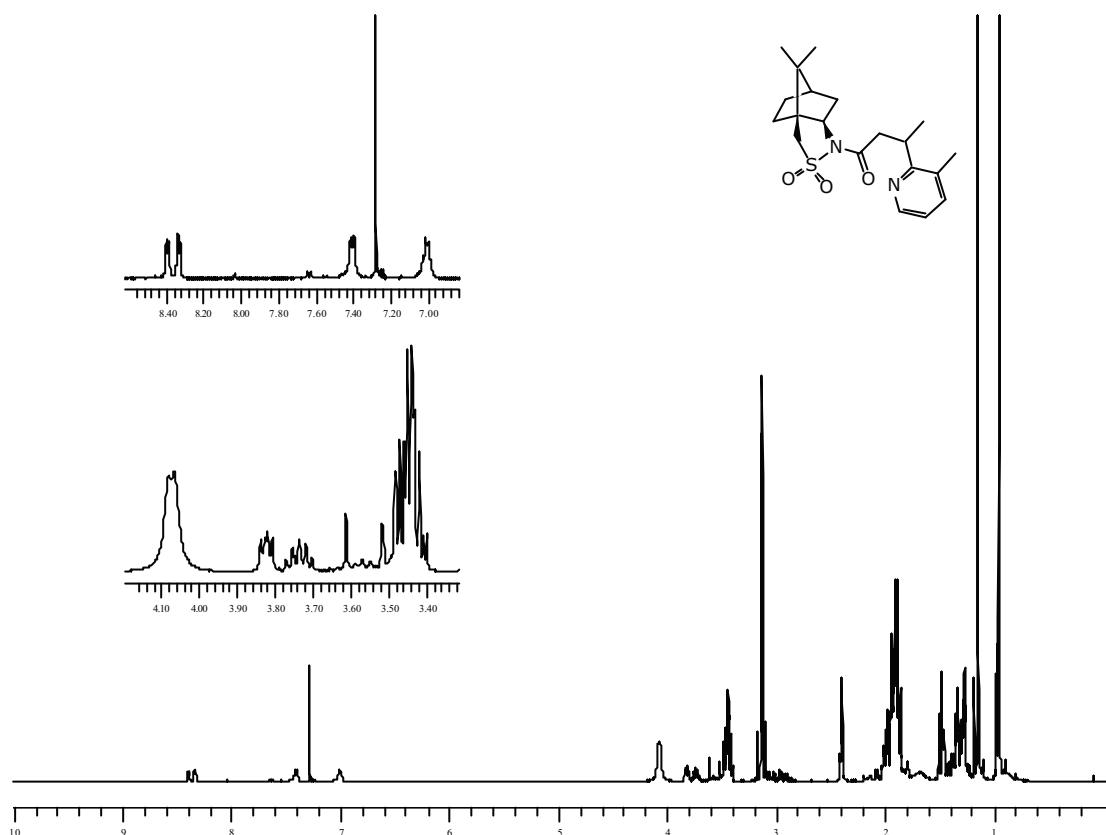
To a suspension of NaH (60% in mineral oil, 83 mg, 2.1 mmol) in toluene (2.5 mL) was added a solution of (2R)-bornane-10,2-sultam (300 mg, 1.4 mmol) in toluene (2.5 mL). The reaction mixture was left to stir at room temperature for 30 min, after which time (E)-crotonoyl chloride (175 mg, 1.7 mmol) in toluene (1 mL) was added slowly and the mixture was stirred for a further 90 min. The resulting mixture was quenched with ice-cold H₂O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo* to give a white hygroscopic solid. Purification by crystallisation from MeOH gave *sulfonamide* **156** (589 mg, 99%) as a white hygroscopic solid. *R_f* 0.60 (nHexane:EtOAc, 1:1); δ_{H} (CDCl₃, 270 MHz) 0.96 (3H, s, CH₃), 1.15 (3H, s, CH₃), 1.34-1.51 (2H), 1.70-1.90 (2H), 1.91 (3H, d, *J* 7.0 Hz, CH₃CH), 2.00-2.15 (1H, m, CH bridgehead), 3.39 (1H, d, *J* 14.0 Hz, CH₂SO₂), 3.47 (1H, d, *J* 14.0 Hz, CH₂SO₂), 3.91 (1H, bt, *J* 6.0 Hz, NCH), 6.56 (1H, dd, *J* 1.5 and 13.5 Hz, CHCO) and 7.06 (1H, sext, *J* 7.0 Hz, CHCH₃). MS

(Cl^+) m/z 284 (MH^+ , 20), 250 (20), 233 (100); HRMS (Cl^+) calcd for $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ (MNH_4^+) 301.1586, found 301.1580 ($\delta = -2.1$ ppm). $[\alpha]_{\text{D}}^{20} -96$ (c. 0.61 in EtOH).

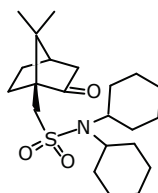
(2*R*, 3'*R*)-(3'-Methylpyridin-2-yl butan-1-one) bornane-10,2-sultam (157a) and (2*R*, 3'*S*)-(3'-methylpyridin-2-yl butan-1-one) bornane-10,2-sultam (157b)



To a solution of 2-bromo-3-methylpyridine (118 μL , 1.1 mmol) in Et_2O (2 mL) at -78°C was added a solution of BuLi (2.5 M in hexanes, 424 μL , 1.1 mmol) and the resulting deep-red solution was stirred for 5 min before cannulation into a solution of copper(I) iodide (101 mg, 0.5 mmol) in dibutylsulfide (185 μL , 1.1 mmol) and Et_2O (2 mL) at 0°C . The resulting dark solution was stirred for 15 min at room temperature before addition of sulfonamide **156** (300 mg, 1.1 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (1 mL) was added and the phases separated. The aqueous layer was extracted with Et_2O (3×5 mL). The organic extracts were combined and extracted with aqueous HCl (2×5 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (EtOAc/hexane, 6:4) afforded sulfonamide **157** (55 mg, 28%, *dr* 49:51, **157a**:**157b** by ^1H NMR) as white hygroscopic solid. R_f 0.66 (Hex/EtOAc, 1:1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3445, 3287, 2959, 2884, 1693 ($\text{C}=\text{O}$), 1645, 1456, 1416, 1392 and 1297; δ_{H} (CDCl_3 , 270 MHz) 0.91 (6H, d, J 7.0 Hz, $2 \times \text{CH}_3\text{CH}$), 1.10 (6H, s, $2 \times \text{CH}_3$), 1.22 (6H, s, $2 \times \text{CH}_3$), 1.69-1.92 (12H, m, $6 \times \text{CH}_2$), 2.34 (3H, s, ArCH_3), 2.35 (3H, s, ArCH_3), 2.89 (4H, dd, J 2.0 and 7.0 Hz, $2 \times \text{CH}_2$), 2.99 (4H, dd, J 2.0 and 7.0 Hz, $2 \times \text{CH}_2$), 3.08 (2H, d, J 2.0, $2 \times \text{CH}$ bridgehead), 3.40-3.83 (8H, $2 \times [\text{CH}_2\text{SO}_2, \text{CONCH}, \text{CHCH}_3]$), 6.95-6.97 (2H, m, $2 \times \text{NCHCH}$), 7.35 (2H, d, J 7.5 Hz, $2 \times \text{NCHCHCH}$), 8.27 (1H, d, J 3.5 Hz, NCH) and 8.33 (1H, d, J 3.5 Hz, NCH); MS (Cl^+) m/z 377 (MH^+ , 80), 378 (30), 379 (10), 233 (100); HRMS (Cl^+) calcd for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$ (MH^+) 377.1909, found 377.1899 ($\delta = -2.7$ ppm).



(10R)-Dicyclohexyl sulfonamide isobornone (158)¹⁶⁵

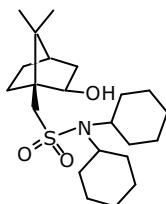


C₂₂H₃₇NO₃S
 Exact Mass: 395.25
 Mol. Wt.: 395.60
 C, 66.79; H, 9.43; N, 3.54; O, 12.13; S, 8.11

To a solution of DMAP (977 mg, 8.0 mmol), NEt₃ (558 μ L, 4.0 mmol), and dicyclohexylamine (1.6 mL, 8.0 mmol) in MeCN (5 mL) at 0 °C was added a solution of (10R)-camphor sulfonyl chloride (1.0 g, 4 mmol) in MeCN (5 mL) and the reaction mixture was left to stir for 1 h. The resulting mixture was diluted with water (10 mL) and extracted with DCM (3 $\times$ 20 mL). The combined organic extracts were washed with citric acid (10%, 100 mL) and brine (100 mL), dried over MgSO₄ and concentrated *in vacuo* to give a white solid. Purification by FC (EtOAc/hexane, 1:9) afforded sulfonamide **158** (700 mg, 45%) as a white hygroscopic solid. *R_f* 0.78 (nHexane:EtOAc, 1:1); δ_{H} (CDCl₃, 270 MHz) 0.86 (3H, s, CH₃), 1.17 (3H, s, CH₃), 0.95-1.63 (6H, m), 1.60-1.78 (16H, m), 1.85 (1H, d, *J* 13.0, CH₂SO₂), 2.04 (2H, d, m, CH₂), 2.33 (1H, dt, *J* 4.0 and 18.0 Hz, COCH), 2.58 (1H, dt, *J* 4.0 and 18.0 Hz, COCH), 2.76 (1H, d, *J* 14.0, CH₂SO₂), 2.29 (1H, d, *J* 14.0, CH₂SO₂) and 3.20-3.39 (1H, m, CH₂). MS (CI⁺) *m/z* 396 (MH⁺, 80), 396

(MNH_4^+ , 50), 331 (20), 314 (20), 233 (10), 217 (15), 200 (20), 182 (15); HRMS (CI^+) calcd for $\text{C}_{22}\text{H}_{38}\text{NO}_3\text{S}$ (MNH_4^+) 396.2572, found 396.2566 ($\delta = -0.7$ ppm). $[\alpha]_{\text{D}}^{20} -29.7$ (c. 0.35 in EtOH).

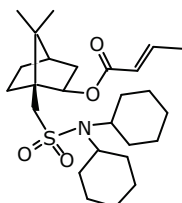
(10*R*)-Dicyclohexyl sulfonamidoisoborneol (159**)**¹⁶⁵



$\text{C}_{22}\text{H}_{39}\text{NO}_3\text{S}$
Exact Mass: 397.27
Mol. Wt.: 397.62
C, 66.45; H, 9.89; N, 3.52; O, 12.07; S, 8.06

To a solution of *sulfonamide* **158** (640 mg, 1.6 mmol) in THF (10 mL) at -78°C was added L-selectride (1.0 M in THF, 1.8 mL, 1.8 mmol) and the reaction mixture was left to stir for 1 h. The resulting mixture was warmed to 0°C and quenched by successive slow additions of H_2O (5 mL), EtOH (5 mL), NaOH (1M, 5 mL) and H_2O_2 (30% in H_2O , 5 mL). The aqueous phase was saturated with K_2CO_3 and extracted with $\text{Et}_2\text{O}:\text{THF}$ (1:1, 3×50 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO_4 and concentrated *in vacuo* to give an off-white solid. Purification by FC (EtOAc/hexane, 1:9) afforded *sulfonamide* **159** (612 mg, 95%) as a white hygroscopic solid. R_f 0.12 (nHexane:EtOAc, 1:1); δ_{H} (CDCl_3 , 270 MHz) 0.78 (3H, s, CH_3), 1.10 (3H, s, CH_3), 0.83-1.98 (26H, m, NCy, $3 \times \text{CH}_2$), 2.64 (1H, d, J 13.0, CH_2SO_2), 3.23 (1H, d, J 13.0, CH_2SO_2), 3.19-3.25 (2H, m, $3 \times \text{NCH}$), 3.49 (1H, d, J 4.0 Hz, CH bridgehead) and 4.05-4.08 (1H, m, CHOH). MS (CI^+) m/z 398 (MH^+ , 80), 380 (60), 182 (90), 123 (100); HRMS (CI^+) calcd for $\text{C}_{22}\text{H}_{40}\text{NO}_3\text{S}$ (MH^+) 398.2729, found 398.2714 ($\delta = -3.8$ ppm). $[\alpha]_{\text{D}}^{20} -24.2$ (c. 0.48 in EtOH).

(10*R*)-O-[(*E*)-2-Butenoyl] dicyclohexyl sulfonamidoisoborneol (160**)**¹⁶⁵

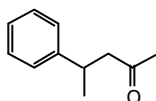


$\text{C}_{26}\text{H}_{43}\text{NO}_4\text{S}$
Exact Mass: 465.29
Mol. Wt.: 465.69
C, 67.06; H, 9.31; N, 3.01; O, 13.74; S, 6.89

To a solution of silver cyanide (570 mg, 3.8 mmol) and *alcohol* **159** (751 mg, 1.9 mmol) in benzene (15 mL) was added (*E*)-crotonyl chloride (202 μL , 2.1 mmol)

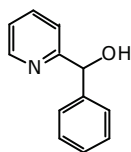
and the reaction mixture was left to stir at 80 °C for 3 h. The resulting mixture was cooled to room temperature and diluted with pentane (20 mL), filtered through a pad of celite, and washed successively with sodium hydrogencarbonate (10% in H₂O, 100 mL) and H₂O (100 mL) dried over CaSO₄. Purification by distillation (150-151 °C/1 atm) afforded *O*-acyl sulfonamide **160** (549 mg, 62%) as a colourless oil. *R*_f 0.41 (CHCl₃:Et₂O, 3:1); δ_{H} (CDCl₃, 270 MHz) 0.83 (3H, s, CH₃), 0.94 (3H, s, CH₃), 1.20-2.01 (31H, m), 2.65 (1H, d, *J* 13.5 Hz, CH₂SO₂), 3.19-3.29 (2H, m, CH₂), 3.26 (1H, d, *J* 13.5 Hz, CH₂SO₂), 5.04 (1H, CHCOCO), 6.78 (1H, d, *J* 16.0 Hz, CHCO) and 6.89-7.23 (1H, m, CHCH₃). MS (CI⁺) *m/z* 483 (MNH₄⁺, 100); HRMS (CI⁺) calcd for C₂₆H₄₇N₂O₄S (MNH₄⁺) 483.3257, found 483.3244 (? = - 2.7 ppm). $[\alpha]_{\text{D}}^{20}$ -35.8 (c. 0.76 in EtOH).

4-Phenylpentan-2-one (**161**).⁸⁵



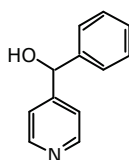
C₁₁H₁₄O
 Exact Mass: 162.10
 Mol. Wt.: 162.23
 C, 81.44; H, 8.70; O, 9.86

A solution of CuBr.SMe₂ (5.7 mg, 0.03 mmol) and Josiphos ligand (17 mg, 0.03 mmol) in tBuOMe (1 mL) was stirred at room temperature for 20 min. 3-penten-2-one (59 µL, 0.61 mmol) was added and then the reaction mixture stirred for a further 5 min, after which time the mixture was cooled to -75 °C. Phenyl magnesium bromide (184 µL, 0.55 mmol) was added and the reaction mixture stirred for a further 2 h. MeOH (500 µL) was added and the reaction mixture slowly warmed to room temperature. The reaction mixture was quenched with saturated aqueous NH₄Cl (500 µL). The resulting mixture was diluted with H₂O (500 µL) and extracted with Et₂O (3 × 500 µL). The combined organic extracts were washed with brine (2 mL), dried over MgSO₄ and concentrated *in vacuo* to give ketone **161** (54 mg, 60%) as a colourless oil. *R*_f 0.33 (Pentane/Et₂O, 9:1); δ_{H} (CDCl₃, 270 MHz) 1.25 (3H, d, *J* 7.0 Hz, CH₃CH), 2.05 (3H, s, CH₃CO), 2.65 (1H, dd, 8.0 and 16.0 Hz, CH₂), 2.73 (1H, dd, 8.0 and 16.0 Hz, CH₂), 3.29 (1H, sextet, *J* 7.0 CH) and 7.18-7.26 (5H, ArH); MS (CI⁺) *m/z* 163 (MH⁺, 20), 180 (MNH₄⁺, 100); HRMS (CI⁺) calcd for C₁₁H₁₈NO (MNH₄⁺) 180.1388, found 180.1385 (? = - 1.9 ppm).

(±)-Phenylpyridin-2-ylmethanol (164**).**¹⁶⁸

C₁₂H₁₁NO
 Exact Mass: 185.08
 Mol. Wt.: 185.22
 C, 77.81; H, 5.99; N, 7.56; O, 8.64

To a solution of *2-iodopyridine* (20 mg, 0.1 mmol) in THF (250 μ L) at room temperature was added a solution of EtMgBr (1.0 M in THF, 108 μ L, 0.1 mmol). The resultant solution was left to stir for 30 min, after which time a solution of *benzaldehyde* (20 μ L, 0.2 mmol) in THF (250 μ L) was added dropwise. The reaction mixture was left to stir for 1 h at room temperature, after which time the reaction mixture was quenched with saturated aqueous NH₄Cl (500 μ L). The resulting mixture was diluted with H₂O (500 μ L) and extracted with Et₂O (3 $\times$ 500 μ L). The combined organic extracts were washed with brine (2 mL), dried over MgSO₄ and concentrated *in vacuo* to give *alcohol* **164** (16.5 mg, 92%) as a colourless oil. *R*_f 0.39 (nHexane/EtOAc, 90:10); δ_{H} (CDCl₃, 270 MHz) 5.32 (1H, bs, OH), 5.72 (1H, bs, CHOH), 7.05–7.41 (7H, ArH), 7.61 (1H, t, *J* 7.5, NCHCHCH) and 8.55 (1H, bs, NCH); MS (CI⁺) *m/z* 186 (MH⁺, 100), 187 (30), 185 (30); HRMS (CI⁺) calcd for C₁₂H₁₁NO (MH⁺) 186.0919, found 186.0916 (? = + 1.6 ppm).

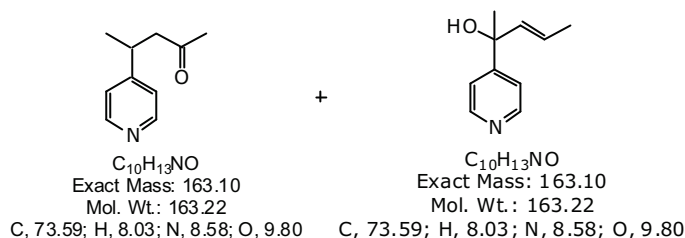
(±)-Phenylpyridin-4-ylmethanol (165**).**¹⁶⁸

C₁₂H₁₁NO
 Exact Mass: 185.08
 Mol. Wt.: 185.22
 C, 77.81; H, 5.99; N, 7.56; O, 8.64

To a solution of *4-iodopyridine* **99** (20 mg, 0.1 mmol) in THF (250 μ L) at room temperature was added a solution of EtMgBr (1.0 M in THF, 108 μ L, 0.1 mmol). The resultant solution was left to stir for 30 min, after which time a solution of *benzaldehyde* (20 μ L, 0.2 mmol) in THF (250 μ L) was added dropwise. The reaction mixture was left to stir for 1 h at room temperature, after which time the reaction mixture was quenched with saturated aqueous NH₄Cl (500 μ L). The resulting mixture was diluted with H₂O (500 μ L) and extracted with Et₂O (3 $\times$ 500 μ L). The combined organic extracts were washed with brine (2 mL), dried over MgSO₄ and concentrated *in vacuo* to give *alcohol* **165** (17.0 mg, 94%) as a colourless oil. *R*_f 0.23 (nHexane/EtOAc, 50:50); δ_{H} (CDCl₃, 270 MHz) 3.38 (1H,

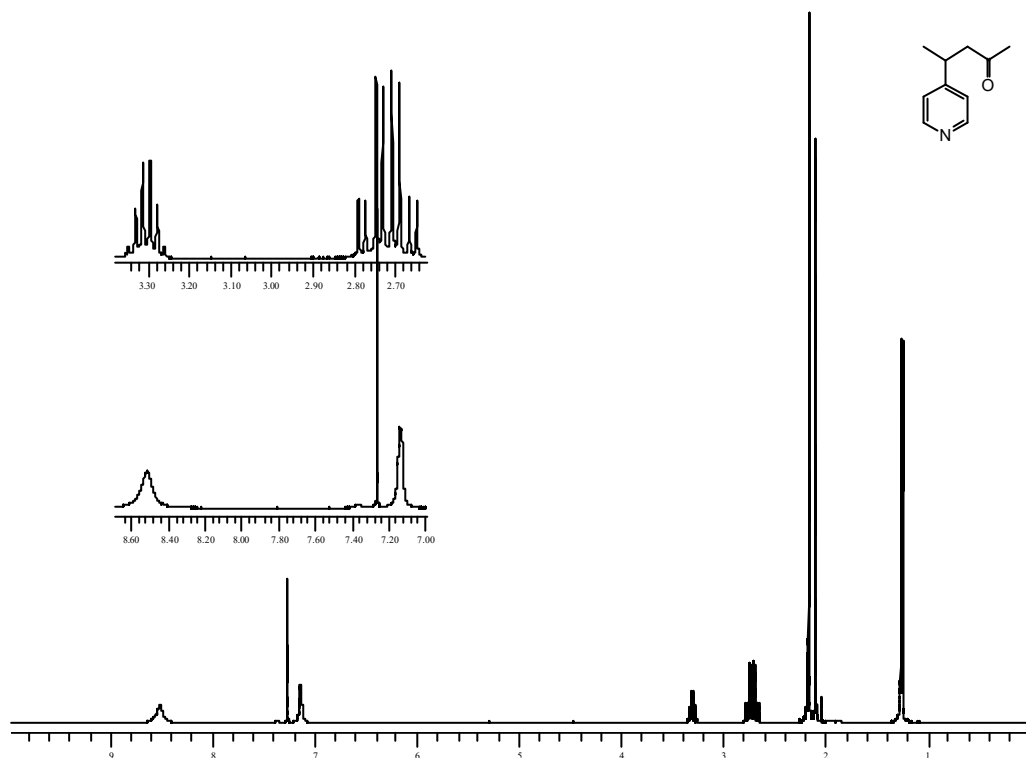
bs, OH), 5.72 (1H, s, *CHOH*), 7.05-7.44 (7H, ArH) and 8.47 (2H, bs, NCH); MS (CI^+) m/z 186 (MH^+ , 100), 184 (90), 109 (20); HRMS (CI^+) calcd for $\text{C}_{12}\text{H}_{12}\text{NO}$ (MH^+) 186.0919, found 186.0915 ($\delta = -0.4$ ppm).

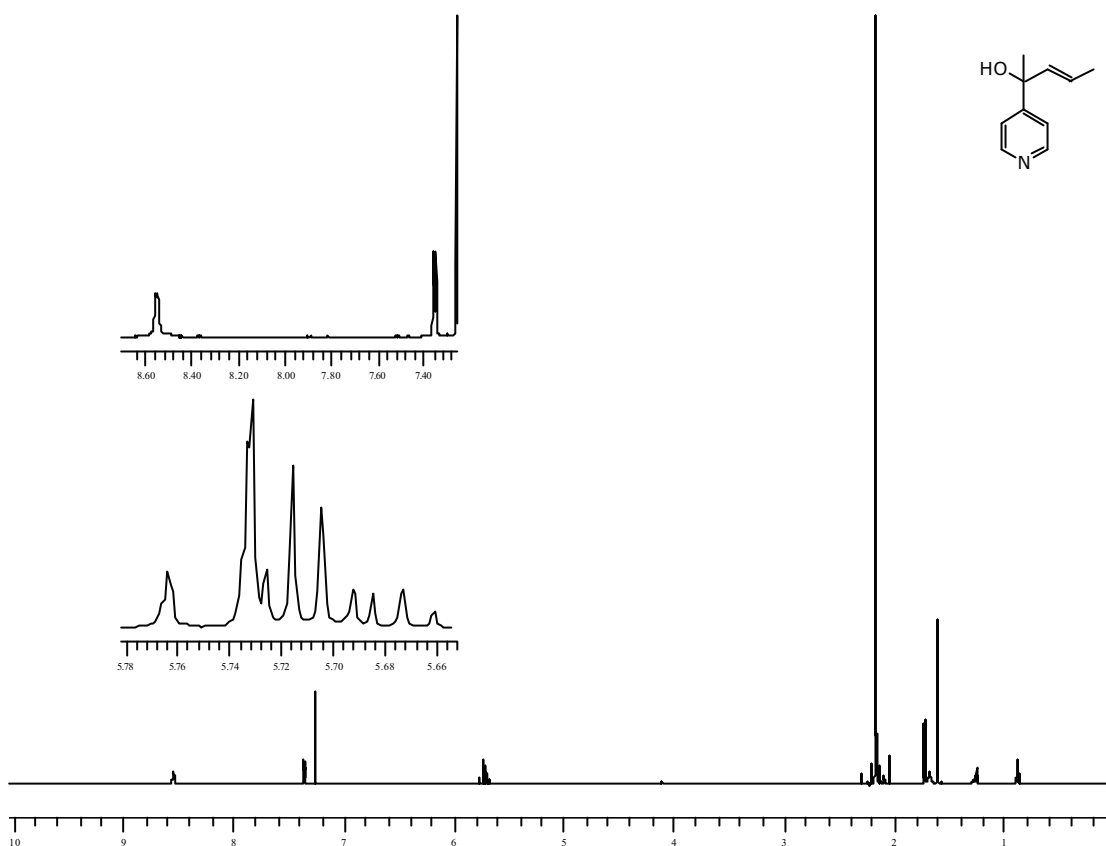
($\pm$)-Pyridin-4-yl-pentan-2-one (166**) and ($\pm$)-Pyridin-4-yl-pent-3-en-2-ol (**167**).**



Method 1: To a solution of $\text{CuBr} \cdot \text{SMe}_2$ (100 mg, 0.6 mmol) and 3-penten-2-one (59 μL , 0.6 mmol) in tBuOMe (1 mL) at 25 $^\circ\text{C}$ was added 2-pyridyl magnesium bromide (184 μL , 0.6 mmol) in Et_2O and the reaction mixture stirred for a 2 h. MeOH (500 μL) was added and the reaction mixture stirred at room temperature for a further 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (500 μL). The resulting mixture was diluted with H_2O (500 μL) and extracted with Et_2O (3×500 μL). The combined organic extracts were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo* to give a colourless oil. Purification by FC ($n\text{Hexane}/\text{EtOAc}$, 90:10) afforded **ketone 166** (53 mg, 54%) as a colourless oil and **alcohol 167** (42 mg, 43%) as a colourless oil. **Ketone 166:** R_f 0.21 (EtOAc); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3418, 2082, 1644 (C=O), 1417, 1361 and 1166; δ_{H} (CDCl_3 , 400 MHz) 1.25 (3H, d, J 7.5 Hz, CH_3CH), 2.09 (3H, s, CH_3CO), 2.67 (1H, dd, J 7.5 and 15.0 Hz, CH_2), 2.76 (1H, dd, J 7.5 and 15.0 Hz, CH_2), 3.27-3.33 (1H, m, PyCH), 7.13 (2H, bs, NCHCH), and 8.50 (2H, bs, NCH); δ_{C} (CDCl_3 , 100 MHz) 21.2 (q), 30.9 (q), 34.4 (t), 50.8 (d), 122.3 (2d), 149.9 (2d), 155.0 (s), and 206.9 (s); MS (CI^+) m/z 164 (MH^+ , 100), 178 (NH_4^+ , 40), 120 (10), 108 (10), 100 (10); HRMS (CI^+) calcd for $\text{C}_{10}\text{H}_{14}\text{NO}$ (MH^+) 164.1073, found 164.1075 ($\delta = -1.5$ ppm). **Alcohol 167:** R_f 0.18 (EtOAc); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3423 (OH), 2954, 2845, 2520, 1655 and 1451; δ_{H} (CDCl_3 , 500 MHz) 1.61 (3H, s, CH_3OH), 1.65 (1H, bs, OH), 1.73 (3H, d, J 6.5 Hz CH_3CH), 5.67-5.77 (2H, 2 $\times$ CH), 7.35 (2H, d, J 6.5 Hz, 2 $\times$ NCHCH) and 8.55 (2H, bs, 2 $\times$ NCH); δ_{C} (CDCl_3 , 125 MHz) 17.7 (q), 29.6 (q), 73.8 (s), 120.3 (d), 125.3 (d), 136.8 (2d), 149.7 (2d), and 156.0 (s); MS (CI^+) m/z 164 (MH^+ , 100), 165 (30), 178 (NH_4^+ , 20); HRMS (CI^+) calcd for $\text{C}_{10}\text{H}_{14}\text{NO}$ (MH^+) 164.1075, found 164.1077 ($\delta = +0.2$ ppm).

Method 2: To a solution of 4-iodopyridine **99** (300 mg, 1.5 mmol) in Et₂O (12.5 mL) at -78 °C was added a solution of BuLi (2.5 M in hexanes, 584 µL, 1.5 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (105 mg, 0.7 mmol) in dibutylsulfide (255 µL, 1.5 mmol) and Et₂O (15 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of 3-penten-2-one (142 µL, 1.5 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (2 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 × 30 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 30 mL, 2 M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (EtOAc) afforded **ketone 166** (102 mg, 86%) as a colourless oil. Spectroscopic data as above.





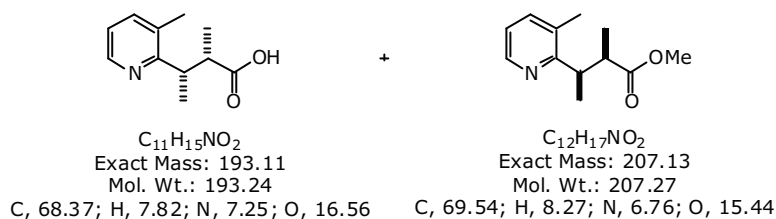
2-Iodo-3-methylpyridine (**168**).¹⁷⁹



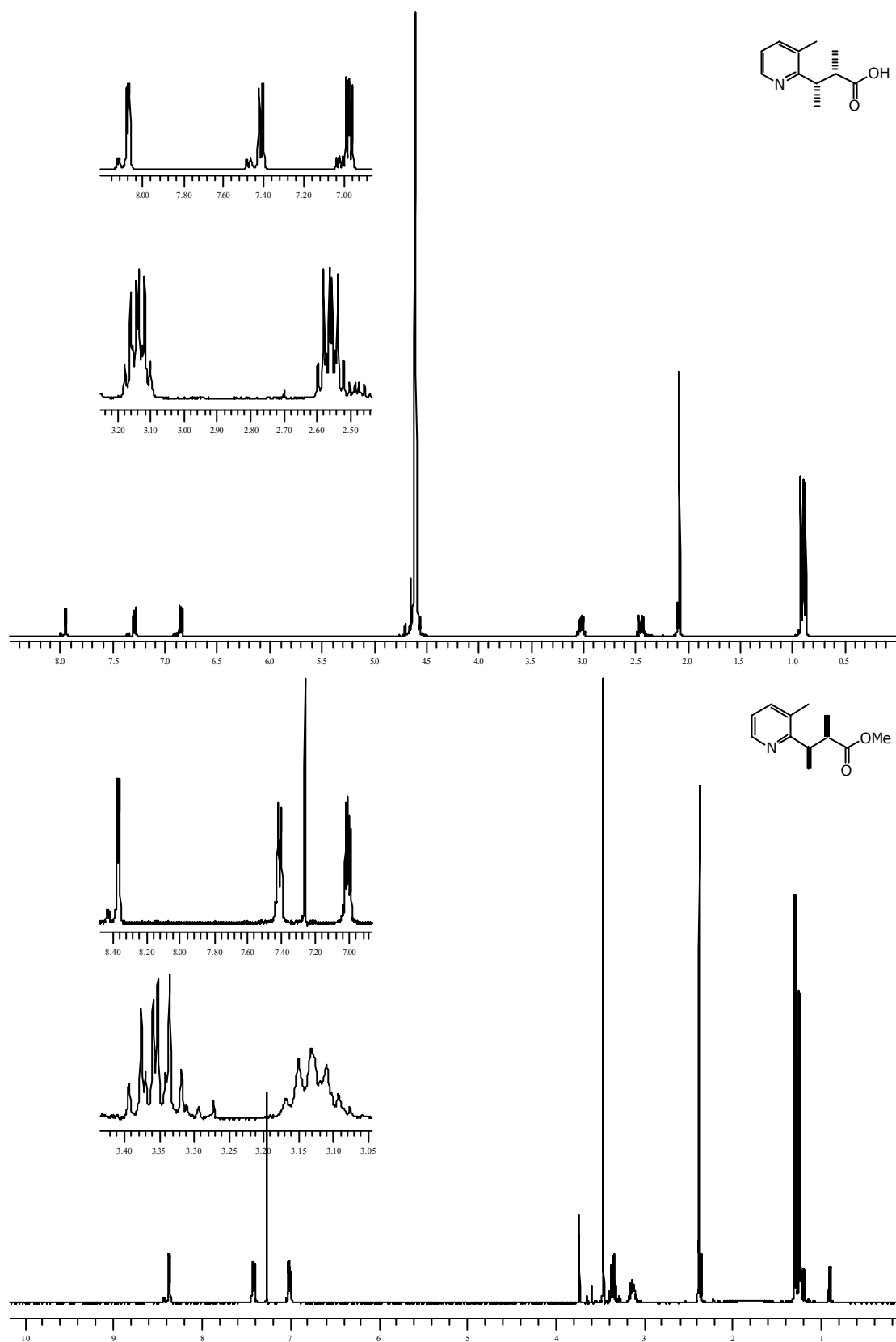
C₆H₆I₁N
 Exact Mass: 218.95
 Mol. Wt.: 219.02
 C, 32.90; H, 2.76; I, 57.94; N, 6.40

To a solution of *2-bromo-3-methylpyridine* (500 mg, 2.9 mmol) in THF (20 mL) was added a solution of *n*-BuLi (2.3 M in hexanes, 1.4 mL, 3.2 mmol). The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and then a solution of MeI (92.7 μL , 1.5 mmol) in THF (2 mL) was added dropwise. The reaction mixture was left to stir for 36 h at $-78\text{ }^{\circ}\text{C}$, after which time the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL). The resulting mixture was diluted with H_2O (500 μL) and extracted with Et_2O ($3 \times 50\text{ mL}$). The combined organic extracts were washed with brine (100 mL), dried over MgSO_4 and concentrated *in vacuo* to give *iodide 168* (602 mg, 95%) as a pale yellow oil. R_f 0.21 (hexane/EtOAc, 9:1); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3044, 2922, 1572, 1453, 1386 and 1041; δ_{H} (CDCl_3 , 500 MHz) 2.35 (3H, s, CH_3), 7.13 (1H, dd, J 5.0 and 7.5 Hz, NCHCH), 7.40 (1H, dd, J 2.0 and 7.5 Hz, NCHCHCH) and 8.13 (1H, dd, J 2.0 and 5.0 Hz, NCH); δ_{C} (CDCl_3 , 125 MHz) 26.3(q), 122.9(d), 125.5(s), 136.8(d), 139.2(s), and 147.8(d); MS (CI^+) m/z 220 (MH^+ , 100), 185 (40), 148 (40), 109 (50); HRMS (CI^+) calcd for $\text{C}_6\text{H}_7\text{N}^{127}\text{I}$ (MH^+) 219.9623, found 219.9627 ($\delta = 0.4\text{ ppm}$).

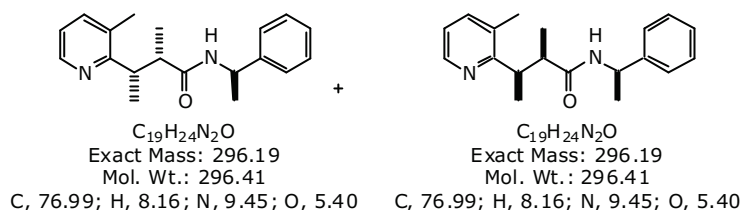
(2S, 3S)-2-Methyl-3-(3'-methyl-pyridin-2'-yl) butyric acid (-)-(154) and **(2R, 3R) -2-methyl-3-(3'-methyl-pyridin-2'-yl) butyric acid methyl ester (+)-(139).**



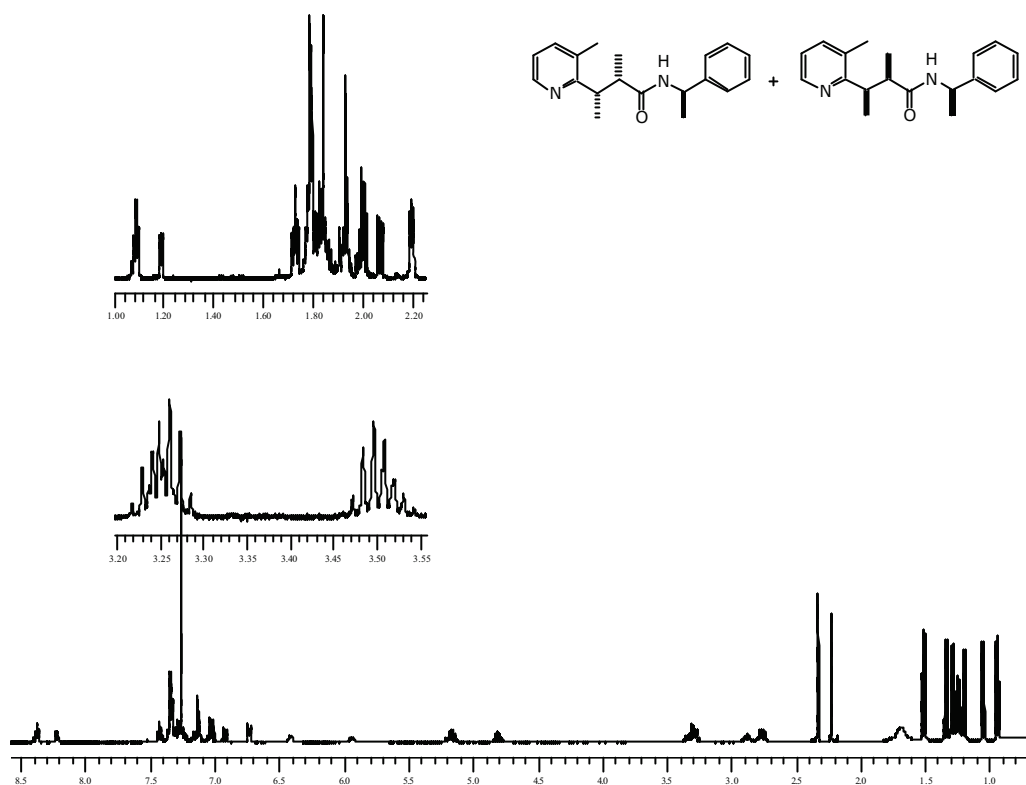
To a suspension of ester **139s** (*dr* 96:4, **139s:139s**) (150 mg, 0.72 mmol) in pH 7.0 phosphate buffer (100 μL) was added lipase *P. florencens* (10 mg, 0.01 mmol) and the mixture was incubated at 30 $^{\circ}\text{C}$ for 48 h. The reaction mixture was filtered through celiteTM and extracted with EtOAc, dried over MgSO_4 and concentrated *in vacuo* to give acid **(-)-154** and ester **(+)-139** as an approx. 50:50 mix of products as defined by ^1H NMR. Purification by partitioning between EtOAc and H_2O . The aqueous layer was concentrated *in vacuo* to give acid **(-)-154** (66 mg, 92%) as a semi-solid and the organic layer was concentrated *in vacuo* to give ester **(+)-139** (69 mg, 97%) as a pale yellow oil. **Acid (-)-154**: *Rf* 0.53 ($\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 90:10); δ_{H} (CDCl_3 , 400 MHz) 1.14 (3H, d, *J* 8.0 Hz, NCHCH_3), 1.17 (3H, d, *J* 8.0 Hz, COOHCHCH_3), 2.35 (3H, s, ArCH_3), 2.68-2.76 (1H, m, CHCOOH), 3.27-3.35 (1H, m, PyCH), 7.10-7.13 (1H, dd, *J* 8.0 and 5.0 Hz, NCHCH), 7.54 (1H, dd, *J* 5.0 and 8.0 Hz, NCHCHCH) and 8.22 (1H, d, *J* 5.0 Hz, NCH); $[\alpha]_{\text{D}}^{20}$ -31.9 (c. 0.69 in H_2O). The organic layer was concentrated *in vacuo* to give Ester **(+)-139**: *Rf* 0.21 (hexane/EtOAc, 90:10); δ_{H} (CDCl_3 , 400 MHz) 1.17 (3H, d, *J* 7.0 Hz, CH_3CHC), 1.28 (3H, d, *J* 7.0 Hz, CH_3CHCO), 2.36 (3H, s, ArCH_3), 3.06-3.12 (1H, m, CHCO_2CH_3), 3.31-3.36 (1H, m, PyCH), 3.44 (3H, s, OCH_3), 6.97 (1H, dd, *J* 5.0 and 7.5 Hz, NCHCH), 7.36 (1H, d, *J* 7.5 Hz, NCHCHCH) and 8.35 (1H, d, *J* 5.0 Hz, NCH); $[\alpha]_{\text{D}}^{20}$ +30.2 (c. 0.66 in CHCl_3).



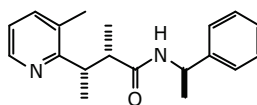
(1''*R*, 2*S*, 3*S*)-2-Methyl-3-(3'-methylpyridin-2'-yl)-*N*-(1-phenylethyl) butyramide and (1''*R*, 2*R*, 3*R*)-2-methyl-3-(3'-methylpyridin-2'-yl)-*N*-(1-phenylethyl) butyramide (169**).**



To a suspension of *acid* **154** (50 mg, 0.3 mmol) and 2-chloro-*N*-methyl-pyridine (79 mg, 0.3 mmol) in dichloromethane (500 μL) was added, (*R*)-phenylethylamine (66 μL , 0.5 mmol) and triethylamine (145 μL , 1.0 mmol) in dichloromethane (500 μL) and the resultant solution was heated to reflux for 5 h. The reaction mixture was concentrated in *vacuo* to give a yellow hygroscopic solid. Purification by FC (EtOAc/nHexane, 50:50) afforded *amides* **169a** and **169b** (74 mg, 83%, *dr* 48:52 **169a**:**169b** by ^1H NMR) as a yellow oil. *R_f* 0.56 (nHexane/EtOAc, 50:50); ν_{max} / cm^{-1} (neat) 3288, 2971, 1644, 1537, 1450 and 1285; **Major**: δ_{H} (CHCl_3 , 400 MHz) 0.91 (3H, d, *J* 7.0 Hz, CONHCHCH_3), 1.25 (3H, d, *J* 7.0 Hz, CONHCHCH_3), 1.29 (3H, d, *J* 7.0 Hz, PyCHCH_3), 2.39 (3H, s, ArCH_3), 2.79-2.85 (1H, m, C(O)CH), 3.27-3.39 (1H, m, NCCH), 4.77-4.83 (1H, m, HNCH), 5.79 (1H, bd, *J* 7.5 Hz, HNCH), 7.06 (1H, dd, *J* 4.5 and 7.5 Hz, NCHCH), 7.17-7.36 (5H, Ph), 7.45 (1H, bd, *J* 7.5 Hz, NHCHCH) and 8.41 (1H, bd, *J* 4.5 Hz, NCH). δ_{C} (CDCl_3 , 100 MHz) 15.7 (q), 18.2 (q), 19.0 (q), 21.1 (q), 40.0 (d), 46.3 (d), 47.9 (d), 121.3 (d), 126.1 (2d), 127.2 (d), 128.5 (2d), 131.5 (d), 138.2 (s), 143.2 (s), 146.3 (d), 163.4 (s) and 175.1 (s); **Minor**: δ_{H} (CHCl_3 , 400 MHz) 1.05 (3H, d, *J* 7.0 Hz, CONHCHCH_3), 1.19 (3H, d, *J* 7.0 Hz, CONHCHCH_3), 1.33 (3H, d, *J* 7.0 Hz, PhCHCH_3), 2.22 (3H, s, ArCH_3), 2.73-2.79 (1H, m, C(O)CH), 3.26-3.34 (1H, m, PyCH), 5.12-5.21 (1H, m, PhCH), 6.41 (1H, bd, *J* 7.5 Hz, NH), 6.74 (1H, dd, *J* 4.5 and 7.5 Hz, NCHCH), 7.01-7.28 (6H, Ph and NCHCHCH) and 8.22 (1H, bd, *J* 4.5 Hz, NCH). δ_{C} (CDCl_3 , 100 MHz) 16.7 (q), 18.8 (q), 21.6 (q), 22.0 (q), 39.5 (d), 46.6 (d), 48.8 (d), 121.0 (d), 121.3 (s), 125.8 (2d), 126.7 (d), 128.7 (2d), 138.0 (d), 143.2 (s), 146.1 (s), 146.7 (d) and 160.8 (s); MS (CI^+) *m/z* 297 (MH^+ , 100) and 176 (10). HRMS (CI^+) calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}^+$ 297.1967 (MH^+), found 297.1963 (MH^+) (? = + -1.3 ppm).



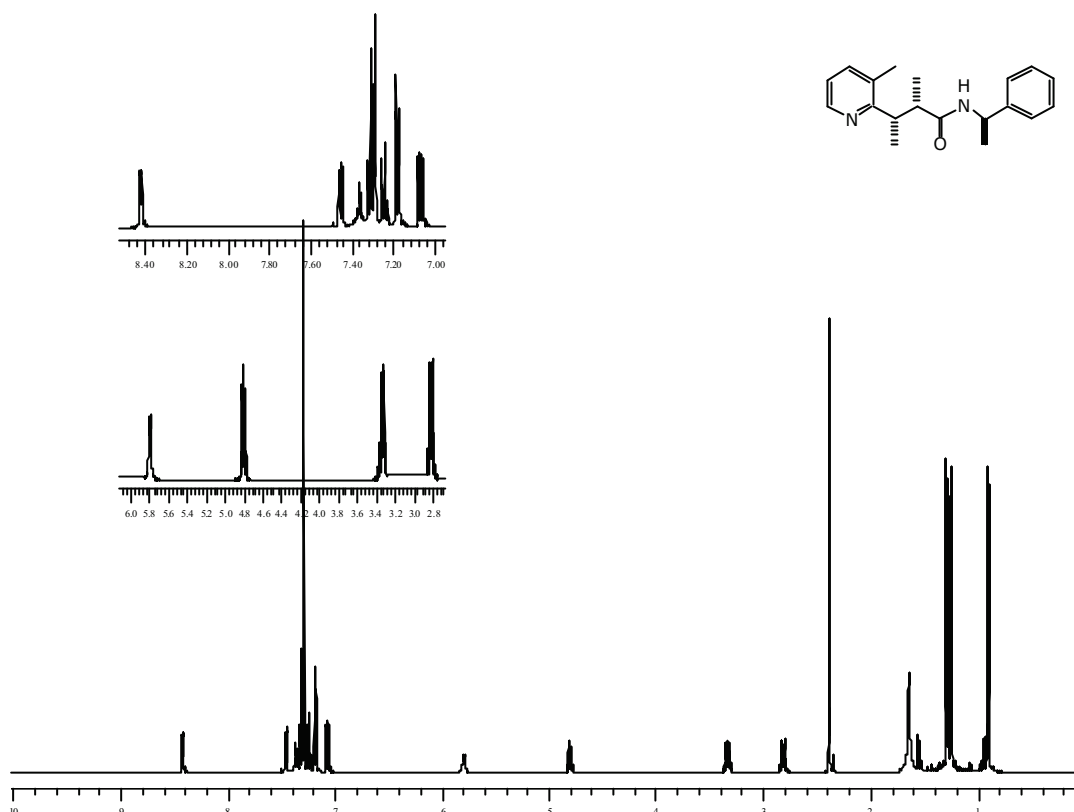
(1''*R*, 2*S*, 3*S*)-2-Methyl-3-(3'-methylpyridin-2'-yl)-*N*-(1-phenylethyl)-butyramide, (169).



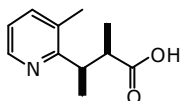
C₁₉H₂₄N₂O
 Exact Mass: 296.19
 Mol. Wt.: 296.41
 C, 76.99; H, 8.16; N, 9.45; O, 5.40

To a suspension of *acid* **(-)-154** (8 mg, 0.04 mmol) and 2-Chloro-*N*-methylpyridine (13 mg, 0.05 mmol) in dichloromethane (100 μ L) was added, (*R*)-*phenylethylamine* (11 μ L, 0.16 mmol) and triethylamine (22 μ L, 0.16 mmol) in dichloromethane (500 μ L) and the resultant solution was heated to reflux for 5 h. The reaction mixture was concentrated in *vacuo* to give a yellow hygroscopic solid. Purification by FC (EtOAc/nHexane, 50:50) afforded *amide* **(-)-169** (8 mg, 73%) as a yellow oil. *R_f* 0.52 (nHexane/EtOAc, 50:50); ν_{max} /cm⁻¹ (neat) 3424, 2350 and 1644; δ_{H} (CHCl₃, 500 MHz) 0.91 (3H, d, *J* 7.0 Hz, CONHCHCH₃), 1.25 (3H, d, *J* 7.0 Hz, CONHCHCH₃), 1.29 (3H, d, *J* 7.0 Hz, PyCHCH₃), 2.39 (3H, s, ArCH₃), 2.79-2.85 (1H, m, C(O)CH), 3.27-3.39 (1H, m, PyCH), 4.77-4.83 (1H, m, PhCH), 5.79 (1H, bd, *J* 7.5 Hz, NH), 7.06 (1H, dd, *J* 4.5 and 7.5 Hz, NCHCH), 7.17-7.36 (5H, Ph), 7.45 (1H, bd, *J* 7.5 Hz, NHCHCH) and 8.41 (1H, bd, *J* 4.5 Hz, NCH). δ_{C} (CDCl₃, 125 MHz) 15.7 (q), 18.2 (q), 19.0 (q), 21.1 (q), 40.0 (d), 46.3 (d), 47.9 (d), 121.3 (d), 126.1 (2d), 127.2 (d), 128.5 (2d), 131.5 (d), 138.2 (s), 143.2 (s), 146.3 (d), 163.4 (s) and 175.1 (s); MS (CI⁺) *m/z* 297 (MH⁺, 100), 283

(10) and 176 (10). HRMS (CI^+) calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}^+$ 297.1967 (MH^+), found 297.1958 (MH^+) ($\delta = -3.0$ ppm). $[\alpha]_{\text{D}}^{20} -78.1$ (c. 0.5 in CHCl_3).

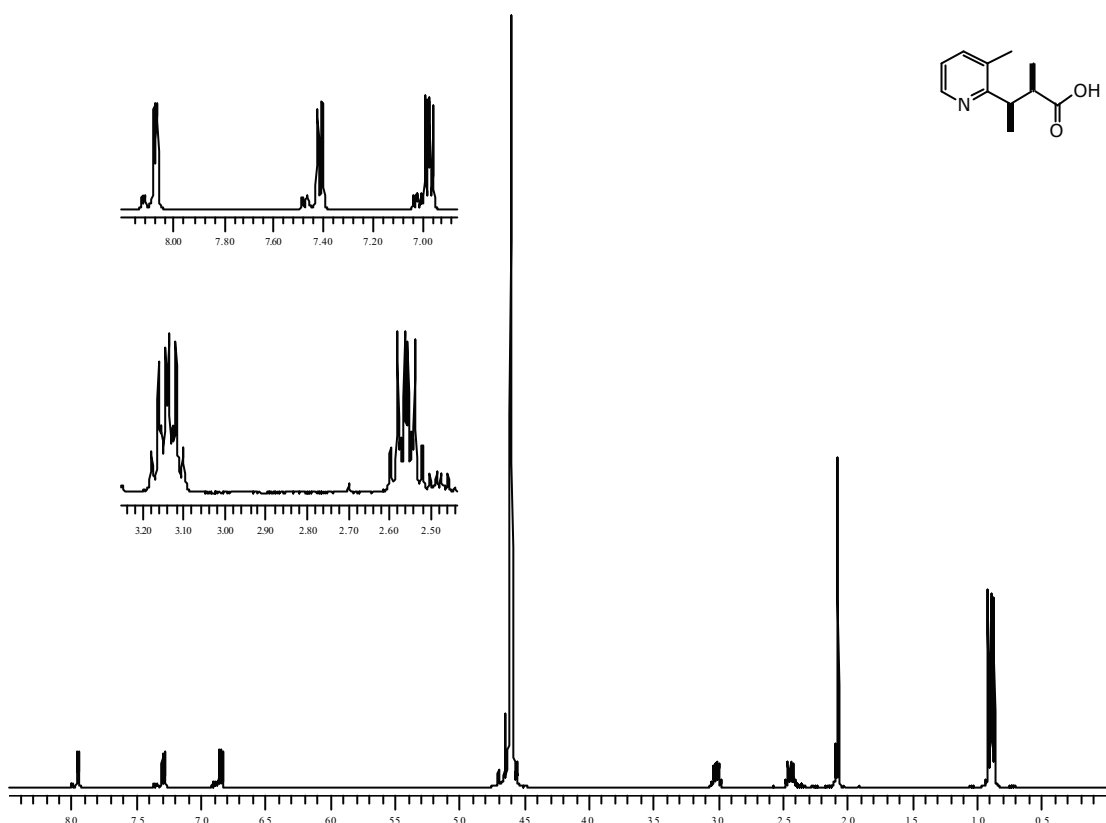


(2R, 3R)-2-Methyl-3-(3'-methylpyridin-2'-yl) butyric acid (154)

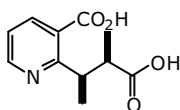


$\text{C}_{11}\text{H}_{15}\text{NO}_2$
 Exact Mass: 193.11
 Mol. Wt.: 193.24
 C, 68.37; H, 7.82; N, 7.25; O, 16.56

To a solution of ester **(+)-139** (66 mg, 0.3 mmol) in methanol (1 mL) was added aqueous NaOH (1 mL, 2 M) and the resulting solution was heated at reflux for 14 h. The reaction mixture was neutralised with aqueous HCl (~1.0 mL, 2 M) and concentrated in *vacuo* to give a white hygroscopic solid. Purification by reverse phase C18 FC (CH_3CN) afforded acid **(+)-154** (59 mg, 95%) a white hygroscopic solid. R_f 0.53 ($\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 90:10); δ_{H} (CDCl_3 , 400 MHz) 1.14 (3H, d, J 8.0 Hz, NCHCH_3), 1.17 (3H, d, J 8.0 Hz, COOHCHCH_3), 2.35 (3H, s, ArCH_3), 2.68–2.76 (1H, m, CHCOOH), 3.27–3.35 (1H, m, PyCH), 7.10–7.13 (1H, dd, J 8.0 and 5.0 Hz, NCHCH), 7.54 (1H, dd, J 5.0 and 8.0 Hz, NCHCHCH) and 8.22 (1H, d, J 5.0 Hz, NCH). $[\alpha]_{\text{D}}^{20} +34$ (c. 0.12 in H_2O).

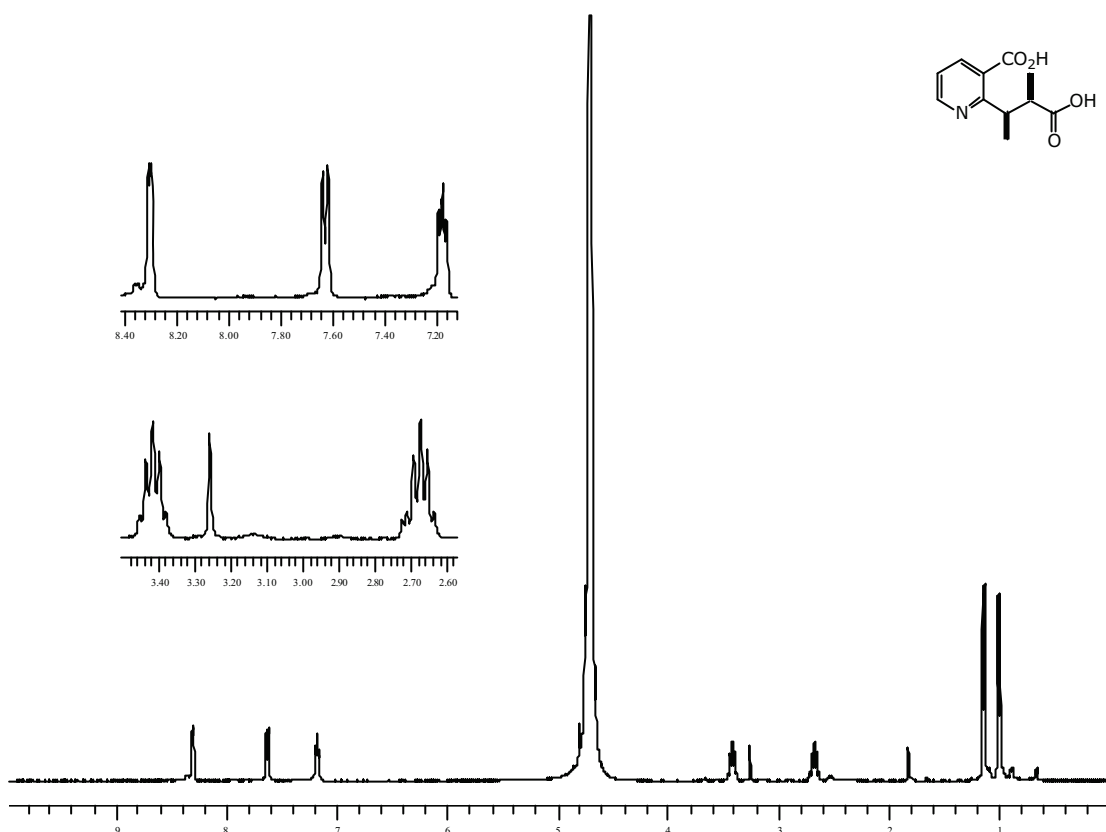


(2R, 3R)- Evoninic acid (4)²²

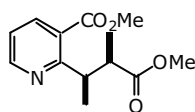


$C_{11}H_{13}NO_4$
 Exact Mass: 223.08
 Mol. Wt.: 223.23
 C, 59.19; H, 5.87; N, 6.27; O, 28.67

To a solution of *acid (+)-154* (60 mg, 0.31 mmol) in H_2O (1 mL) at room temperature was added $KMnO_4$ (123 mg, 0.78 mmol) and the resulting solution was heated at reflux for 14 h. The reaction mixture was filtered and the filtrate was concentrated to $\sim 200 \mu L$. This clear solution was neutralised to pH 7 with aqueous HCl (1 M) to give a white hygroscopic solid. Purification by reverse phase C18 FC (CH_3CN) afforded *evoninic acid (+)-4* (65 mg, 98%) as a white hygroscopic solid. mp 134-137 °C (*cf.* lit.²² 132-136 °C); R_f 0.09 (CH_3CN/H_2O , 90:10); δ_H (D_2O , 400 MHz) 1.04 (3H, d, J 7.0 Hz, $PyCHCH_3$), 1.17 (3H, d, J 7.0 Hz, $COOHCHCH_3$), 2.68-2.76 (1H, m, $CHCOOH$), 3.43-3.51 (1H, m, $PyCH$), 7.20 (1H, dd, J 8.0 and 5.0 Hz, $NCHCH$), 7.65 (1H, dd, J 8.0 and 1.5 Hz, $NCHCHCH$) and 8.33 (1H, dd, J 5.0 and 1.5 Hz, NCH); $[\alpha]_D^{20} +26$ (c. 0.15 in H_2O).



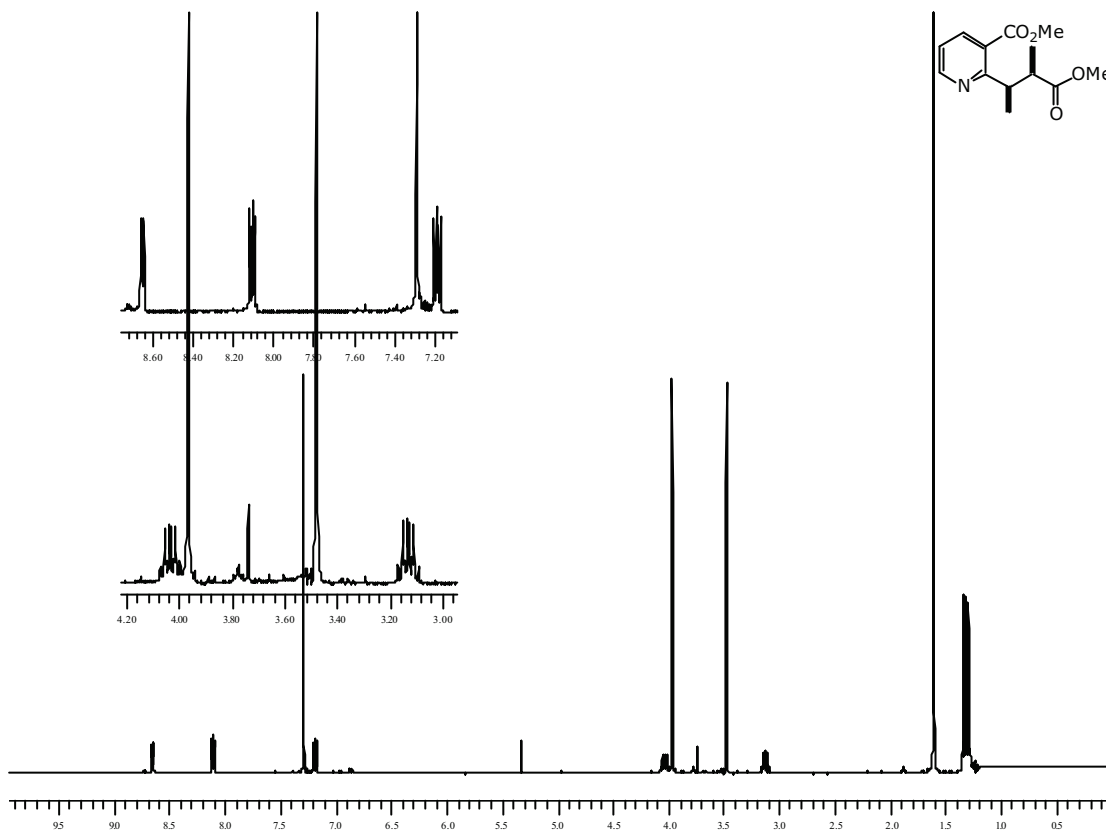
(2R, 3R)-Evoninic acid dimethyl ester (170)²²



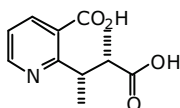
C₁₃H₁₇NO₄
 Exact Mass: 251.12
 Mol. Wt.: 251.28
 C, 62.14; H, 6.82; N, 5.57; O, 25.47

To a solution of *diacid (+)-(4)* (20 mg, 0.1 mmol) in MeOH (500 μ L) at room temperature was added diazomethyltrimethylsilane (2.0 M in Et₂O, 100 μ L, 0.2 mmol) and the resulting solution was stirred until a yellow colour persisted in the reaction mixture. The reaction mixture was quenched with NaHCO₃ and extracted into Et₂O (3 $\times$ 5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (nHexane/EtOAc, 90:10) afforded *dimethyl ester (+)-170* (15.8 mg, 70%) as a colourless oil. *R*_f 0.56 (nHexane:EtOAc, 90:10); ν_{max} /cm⁻¹ (neat) 3422, 2985, 1728 and 1644; δ_{H} (CDCl₃, 400 MHz) 1.30 (3H, d, *J* 7.0 Hz, CH₃), 1.31 (3H, d, *J* 7.0 Hz, CH₃), 3.10-3.15 (1H, m, CHCO₂Me), 3.48 (3H, s, CO₂Me), 3.96 (3H, s, ArCO₂Me), 3.98-4.05 (1H, m, PyCH), 7.18 (1H, dd, *J* 4.5 and 8.0 Hz, NCHCH), 8.10 (1H, dd, *J* 2.0 and 8.0 Hz, NCHCHCH) and 8.65 (1H, dd, *J* 2.0 and 8.0 Hz, NCH). δ_{C} (CDCl₃, 125 MHz) 15.3 (q), 17.9 (q), 40.2 (d), 44.4 (d), 51.3 (q), 52.4 (q), 120.6 (d), 125.6 (s), 138.0 (d), 151.5 (d), 165.6 (s), 167.2 (s) and 176.6 (s); MS (CI⁺) *m/z* 252 (MH⁺, 100). HRMS (CI⁺) calcd for

$C_{13}H_{18}NO_4^+$ 252.1236 (MH^+), found 252.1236 (MH^+) ($\delta = 0.0$ ppm). $[\alpha]_D^{20} +43.3$ (c. 0.15 in $CHCl_3$).

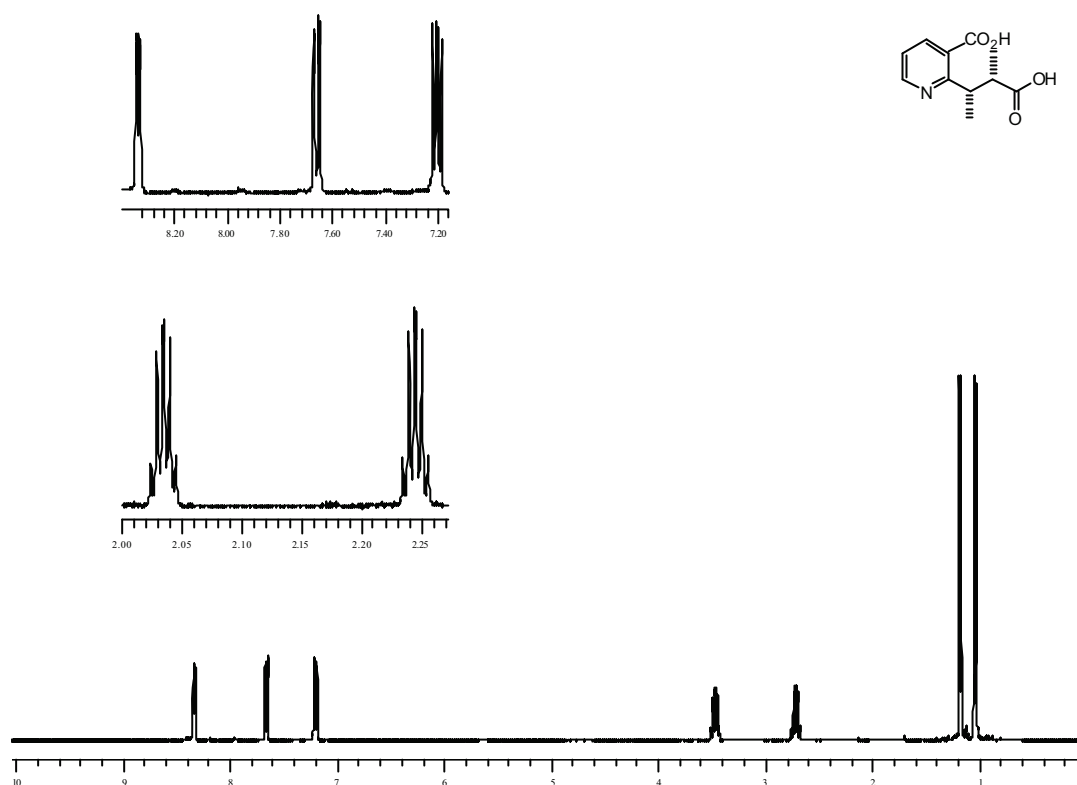


(2S, 3S)-Evoninic acid (4)²²

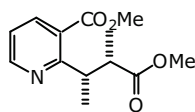


$C_{11}H_{13}NO_4$
Exact Mass: 223.08
Mol. Wt.: 223.23
C, 59.19; H, 5.87; N, 6.27; O, 28.67

To a solution of *acid (-)-154* (60 mg, 0.31 mmol) in H_2O (1 mL) at room temperature was added $KMnO_4$ (123 mg, 0.78 mmol) and the resulting solution was heated at reflux for 14 h. The reaction mixture was filtered and the filtrate was concentrated to ~ 200 μL . This clear solution was neutralised to pH 7 with aqueous HCl (1 M) to give a white hygroscopic solid. Purification by reverse phase C18 FC (CH_3CN) afforded *evoninic acid (-)-(4)* (65 mg, 98%) as a white hygroscopic solid. R_f 0.09 (CH_3CN/H_2O , 90:10); δ_H (D_2O , 400 MHz) 1.04 (3H, d, J 7.0 Hz, $PyCHCH_3$), 1.17 (3H, d, J 7.0 Hz, $COOHCHCH_3$), 2.68-2.76 (1H, m, $PyCH$), 3.43-3.51 (1H, m, $CHCOOH$), 7.20 (1H, dd, J 8.0 and 5.0 Hz, $NCHCH$), 7.65 (1H, dd, J 8.0 and 1.5 Hz, $NCHCHCH$) and 8.33 (1H, dd, J 5.0 and 1.5 Hz, NCH); $[\alpha]_D^{20} -41.2$ (c. 0.14 in H_2O).



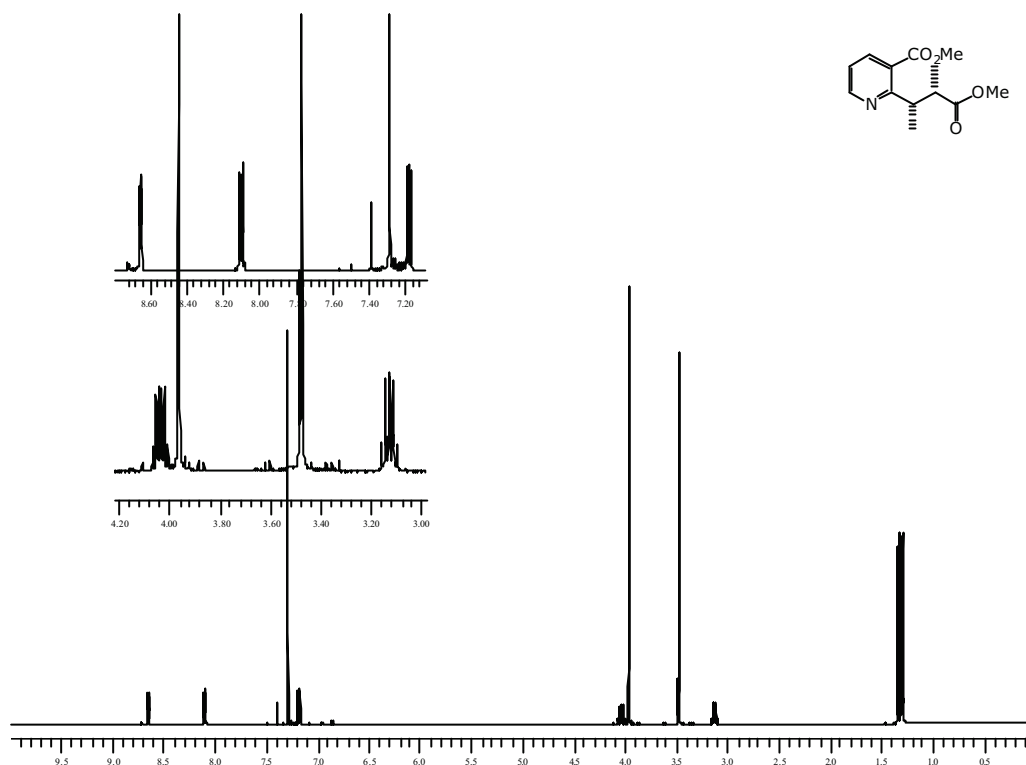
(2S, 3S)-Evonic acid dimethyl ester (170)²²



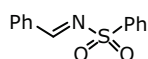
C₁₃H₁₇NO₄
 Exact Mass: 251.12
 Mol. Wt.: 251.28
 C, 62.14; H, 6.82; N, 5.57; O, 25.47

To a solution of *diacid (-)-154* (21 mg, 0.1 mmol) in MeOH (500 μ L) at room temperature was added diazomethyltrimethylsilane (2.0 M in Et₂O, 100 μ L, 0.2 mmol) and the resulting solution was stirred until a yellow colour persisted in the reaction mixture. The reaction mixture was quenched with NaHCO₃ and extracted into Et₂O (3 $\times$ 5 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (nHexane/EtOAc, 90:10) afforded *dimethyl ester (-)-170* (20.1 mg, 85%) as a colourless oil. *R*_f 0.56 (nHexane:EtOAc, 90:10); ν_{max} /cm⁻¹ (neat) 3423, 2625, 1601 and 1638; δ_{H} (CDCl₃, 400 MHz) 1.30 (3H, d, *J* 7.0 Hz, C(O)CHCH₃), 1.31 (3H, d, *J* 7.0 Hz, PyCHCH₃), 3.10-3.15 (1H, m, CHCO₂CH₃), 3.48 (3H, s, CO₂CH₃), 3.96 (3H, s, ArCO₂CH₃), 4.03 (1H, m, PyCH), 7.18 (1H, dd, *J* 4.5 and 8.0 Hz, NCHCH), 8.10 (1H, dd, *J* 2.0 and 8.0 Hz, NCHCHCH) and 8.65 (1H, dd, *J* 2.0 and 8.0 Hz, NCH). δ_{C} (CDCl₃, 125 MHz) 15.2 (q), 17.9 (q), 40.2 (d), 44.4 (d), 51.3 (q), 52.4 (q), 120.6 (d), 125.6 (s), 138.0 (d), 151.5 (d), 165.6 (s), 167.2 (s) and 176.6 (s); MS (CI⁺) *m/z* 252 (MH⁺, 100) and 274 (10).

HRMS (CI^+) calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_4^+$ 252.1236 (MH^+), found 252.1234 (MH^+) ($? = -0.7$ ppm). $[\alpha]_{\text{D}}^{20} -41.1$ (c. 0.14 in CHCl_3). $[\text{Lit}^{22} [\alpha]_{\text{D}}^{20} -42$ (CHCl_3)].



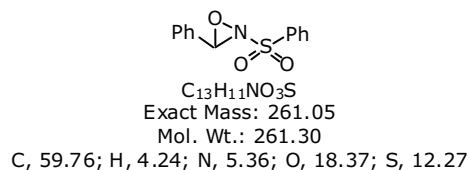
***N*-Benzylidenebenzenesulfonamide (**171**).¹⁸³**



$\text{C}_{13}\text{H}_{11}\text{NO}_2\text{S}$
Exact Mass: 245.05
Mol. Wt.: 245.30

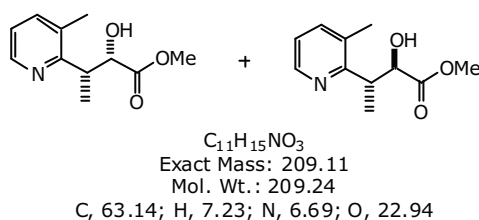
C, 63.65; H, 4.52; N, 5.71; O, 13.04; S, 13.07

A mixture of the *dimethyl acetyl of benzaldehyde* (7.6 g, 50.0 mmol) and sulphonamide (7.9 g, 50.0 mmol) was heated to 150–180 °C in a single-necked flask fitted with a short-path distillation kit. The reaction mixture was heated until all the methanol had ceased distilling over (30 min), at which time the solution was placed under high vacuum and allowed to cool to ambient temperature. The solid was dissolved in a minimum amount of CH_2Cl_2 and precipitated by slow addition of *n*-Pentane to afford *imine* **171** (10.81 g, 88%) as a white amorphous solid. R_f 0.22 (*n*Hexane/EtOAc, 95:5); δ_{H} (CDCl_3 , 400 MHz) 7.45–7.71 (6H, ArH), 7.88–8.09 (4H, ArH) and 9.10 (1H, s, CH); MS (CI^+) m/z 246 (MH^+ , 70), 263 (MNH_4^+ , 80), 192 (20), 175 (100); HRMS (CI^+) calcd for $\text{C}_{13}\text{H}_{12}\text{NO}_2\text{S}$ (MH^+) 246.0589, found 246.0579 ($? = -1.0$ ppm).

2-Benzenesulfonyl-3-phenyloxaziridine (172).¹⁸³

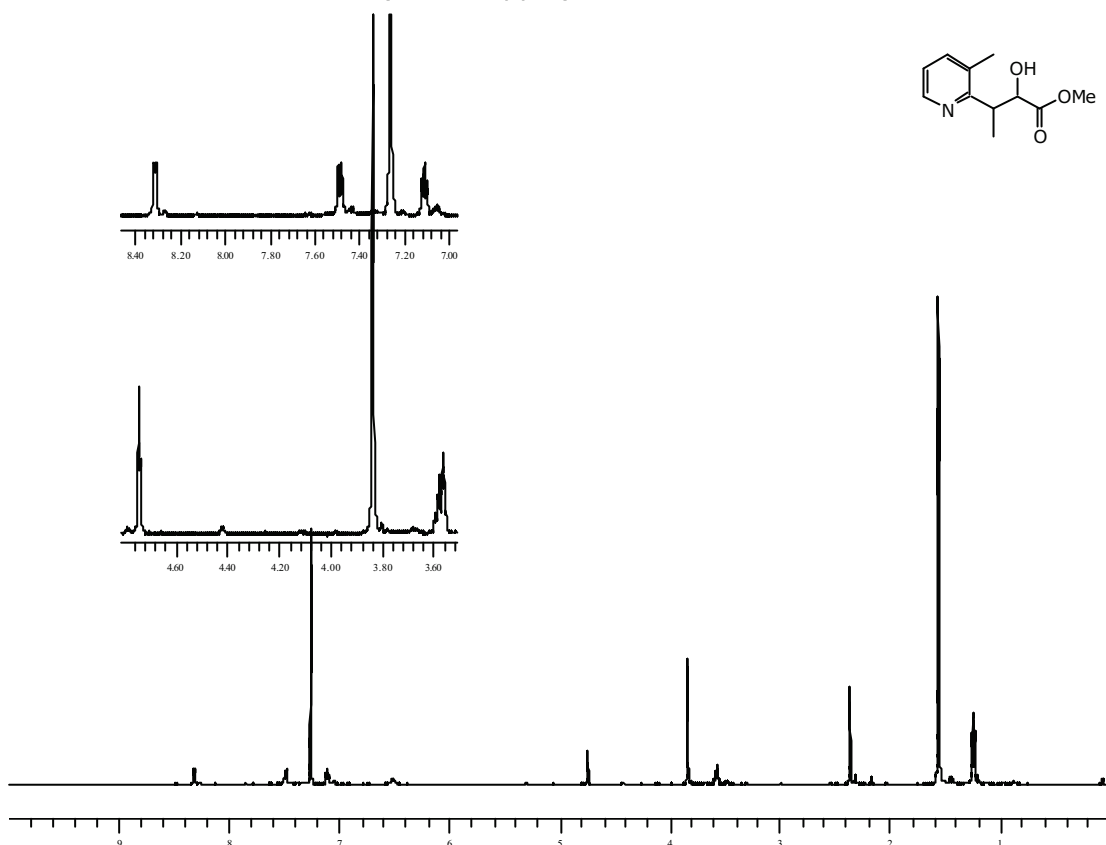
To a cooled (0 °C) solution of *sulfonimine* **171** (500 mg, 2.0 mmol) in $CHCl_3$ (6.5 mL) and $NaHCO_3$ (446 mg, 5.3 mmol) in H_2O (5 mL) was added *m*CPBA (760 mg, 4.4 mmol) in $CHCl_3$ (12.5 mL) dropwise over 45 min. After complete addition the solution was stirred for a further 4 h and the $CHCl_3$ solution washed with 10% Na_2SO_3 (3 × 20 mL) and 10% $NaHCO_3$ (3 × 20 mL). The combined organic extracts were dried over anhydrous K_2CO_3 (30 min – 60 min at 0 °C) the solvent was removed *in vacuo* keeping the bath temperature below 35 °C. The solid was washed with a small amount of *n*-pentane to afford *oxaziridine* **172** (522 mg, 98%) a white amorphous solid. R_f 0.41 (*n*Hexane/EtOAc, 90:10); δ_H ($CDCl_3$, 400 MHz) 5.52 (1H, s, CH), 7.42-7.59 (5H, m, ArH), 7.67 (2H, t, J 7.5 Hz, ArH), 7.78 (1H, t, J 7.5 Hz, ArH) and 8.08 (2H, d, J 7.5 Hz, ArH); MS (CI^+) m/z 279 (MNH_4^+ , 20), 139 (100), 124 (60), 105 (40); HRMS (CI^+) calcd for $C_{13}H_{15}N_2O_3S$ (MNH_4^+) 279.0803, found 279.0800 (δ = - 0.3 ppm).

(±)-syn-2-Hydroxy-3-(3'-methylpyridin-2'-yl) butyric acid methyl ester and **(±)-anti-2-hydroxy-3-(3'-methylpyridin-2'-yl) butyric acid methyl ester (173b and 173a).**

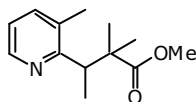


To a solution of KHMDS (0.5 M in toluene, 502 μ L, 0.3 mmol) at -78 °C was added a solution of *ester* **138** (44 mg, 0.2 mmol) in toluene (500 μ L). The reaction mixture was stirred at -78 °C for 1 h, warmed to 0 °C for 1 h and then cooled back to -78 °C and then a solution of oxaziridine (77 mg, 0.3 mmol) in toluene (500 μ L) was added dropwise. The reaction mixture was left to stir for 1 h at -78 °C, slowly warmed to rt for 36 h, after which time the reaction mixture was quenched with saturated aqueous NH_4Cl (100 μ L). The resulting mixture was diluted with H_2O (200 μ L) and extracted with Et_2O (3 × 200 μ L). The combined organic extracts were washed with brine (200 μ L), dried over $MgSO_4$ and concentrated *in vacuo* to give *ester* **173** (38 mg, 80%, *dr* >95:5, unassigned **173a:173b** by 1H NMR) as a colourless oil. R_f 0.43 (hexane/EtOAc, 95:5);

$\nu_{\max}/\text{cm}^{-1}$ (neat) 3442, 2088, 1643 (C=O), 1238 and 1084; δ_{H} (CDCl_3 , 500 MHz) 1.26 (3H, d, J 7.0 Hz, CH_3CH), 2.39 (3H, s, ArCH_3), 3.59 (1H, m, CHCH_3), 3.86 (3H, s, OCH_3), 4.77 (1H, d, J 2.0 Hz, $\text{CH}(\text{OH})$), 6.51 (1H, bs, OH), 7.14 (1H, t, J 5.0 Hz NCHCH), 7.51 (1H, d, J 7.0 Hz, NCHCHCH) and 8.33 (1H, d, J 5.0 Hz, NCH); δ_{C} (CDCl_3 , 100 MHz) 13.8 (q), 18.4 (q), 38.4 (d), 52.3 (d), 73.9 (q), 121.9 (d), 138.7 (d), 145.8 (d), 161.5 (s), 162.2 (s) and 172.5 (s); MS (CI^+) m/z 210 (MH^+ , 100), 211 (20) and 122 (10); HRMS (CI^+) calcd for $\text{C}_{12}\text{H}_{16}\text{NO}_3$ (MH^+) 210.1139, found 210.1130 ($\Delta = 4.2$ ppm).



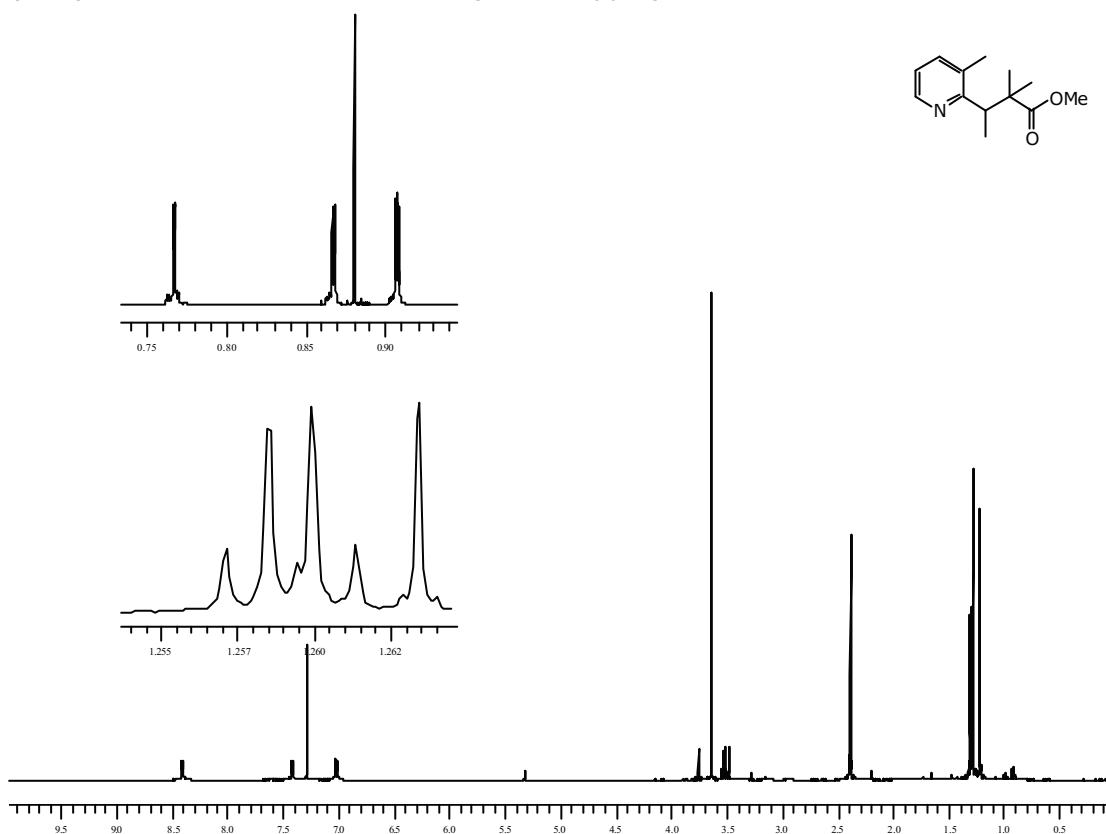
(±)-2,2-Dimethyl-3-(3-methylpyridin-2-yl) butyric acid methyl ester (175)



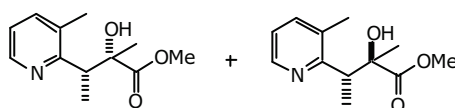
$\text{C}_{13}\text{H}_{19}\text{NO}_2$
Exact Mass: 221.14
Mol. Wt.: 221.30
C, 70.56; H, 8.65; N, 6.33; O, 14.46

To a solution of ester **139** (*dr* 96:4, **139s**:**139a**) (20 mg, 0.1 mmol) in toluene (100 μL) at 22 $^{\circ}\text{C}$ was added a solution of KHMDS (0.5 M in toluene, 198 μL , 0.1 mmol). The reaction mixture was stirred at 22 $^{\circ}\text{C}$ for 2 h, after which a solution of MeI (14 mg, 0.1 mmol) in toluene (100 μL) was added dropwise. The reaction mixture was left to stir at 22 $^{\circ}\text{C}$ for 16 h, after which time the reaction mixture was quenched with saturated aqueous NH_4Cl (100 μL). The resulting mixture was

diluted with H₂O (200 μ L) and extracted with Et₂O (3 $\times$ 200 μ L). The combined organic extracts were washed with brine (200 μ L), dried over MgSO₄ and concentrated *in vacuo* to give ester **175** (21 mg, 97%) as a colourless oil. R_f 0.21 (CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2968, 1730 (C=O), 1571, 1451, 1388, 1254, 1190, 1139, 1107 and 1155; δ_{H} (CDCl₃, 500 MHz) 1.22 (3H, s, CH₃C), 1.28 (3H, s, CH₃C), 1.29 (3H, d, *J* 7.0 Hz, CH₃CH), 2.39 (3H, s, ArCH₃), 3.50 (1H, q, *J* 7.0 Hz, CHCH₃), 3.64 (3H, s, OCH₃), 7.02 (1H, dd, *J* 4.5 and 7.5 Hz, NCHCH), 7.41 (1H, d, *J* 7.5 Hz, NCHCHCH) and 8.41 (1H, dd, *J* 1.0 and 4.5 Hz, NCH); δ_{C} (CDCl₃, 125 MHz) 16.0 (q), 19.6 (q), 22.3 (q), 23.8 (q), 42.7 (d), 46.6 (s), 51.6 (q), 121.1 (d), 131.2 (s), 137.6 (d) 146.4 (d), 161.6 (s) and 178.4 (s); MS (CI⁺) *m/z* 223 (10), 222 (MH⁺, 100), 208 (20) and 121 (20); HRMS (CI⁺) calcd for C₁₃H₂₀NO₂ (MH⁺) 222.1494, found 222.1497 (δ = 1.3 ppm).

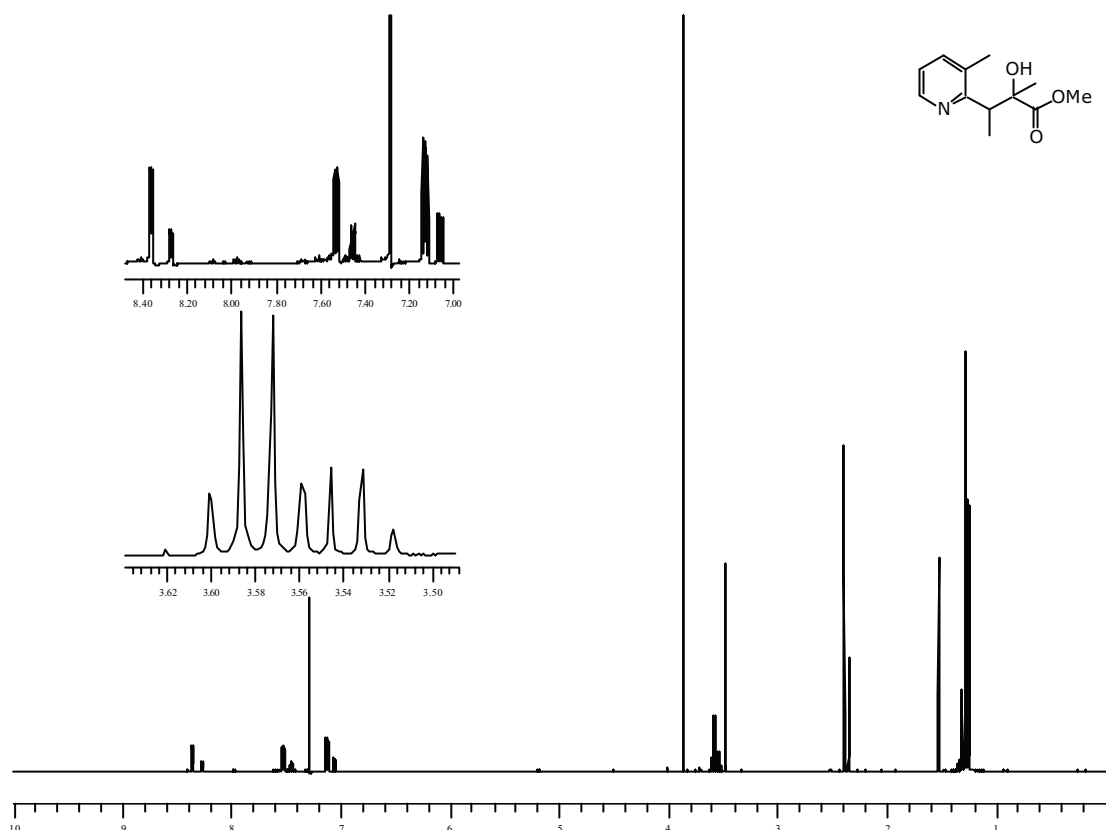


(±)-*syn*-2-Hydroxy-2-methyl-3-(3-methyl-pyridin-2-yl) butyric acid methyl ester and (±)-*anti*-2-hydroxy-2-methyl-3-(3-methyl-pyridin-2-yl) butyric acid methyl ester (176b** and **176a**).**

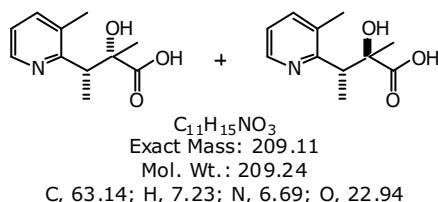


C₁₂H₁₇NO₃
 Exact Mass: 223.12
 Mol. Wt.: 223.27
 C, 64.55; H, 7.67; N, 6.27; O, 21.50

To a solution of ester **139** (*dr* 96:4, **139s:139a**) (19 mg, 0.1 mmol) in toluene (100 μ L) at 22 $^{\circ}$ C was added a solution of KHMDS (0.5 M in toluene, 198 μ L, 0.1 mmol). The reaction mixture was stirred at 22 $^{\circ}$ C for 2 h, after which a solution of oxaziridine (31 mg, 0.1 mmol) in toluene (100 μ L) was added dropwise. The reaction mixture was left to stir at 22 $^{\circ}$ C for 16 h, after which time the reaction mixture was quenched with saturated aqueous NH_4Cl (100 μ L). The resulting mixture was diluted with H_2O (200 μ L) and extracted with Et_2O (3 $\times$ 200 μ L). The combined organic extracts were washed with brine (200 μ L), dried over MgSO_4 and concentrated *in vacuo* to give esters **176** (15.8 mg, 78%, *dr* 75:25, **176a:176b**) as a colourless oil. R_f 0.13 ($\text{CHCl}_3/\text{Et}_2\text{O}$, 95:5); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2930, 1729, 1459 (C=O), 1251 and 1092; **Major**: δ_{H} (CDCl_3 , 500 MHz) 1.25 (3H, d, J 7.0 Hz, CH_3CH), 1.28 (3H, s, $\text{CH}_3\text{C}(\text{OH})$), 2.39 (3H, s, ArCH_3), 3.58 (1H, q, J 7.0 Hz, CHCH_3), 3.86 (3H, s, OCH_3), 7.13 (1H, dd, J 4.5 and 7.5 Hz NCHCH), 7.54 (1H, d, J 7.5 Hz, NCHCHCH) and 8.36 (1H, dd, J 1.5 and 4.5 Hz, NCH); δ_{C} (CDCl_3 , 125 MHz) 16.5 (q), 18.8 (q), 26.7 (d), 41.5 (d), 52.4 (q), 78.3 (s), 121.8 (d), 131.7 (s), 138.8 (d), 145.8 (d), 161.8 (s) and 175.7 (s); **Minor**: δ_{H} (CDCl_3 , 500 MHz) 1.32 (3H, d, J 7.0 Hz, CH_3CH), 1.52 (3H, s, $\text{CH}_3\text{C}(\text{OH})$), 2.35 (3H, s, ArCH_3), 3.48 (3H, s, OCH_3), 3.54 (1H, q, J 7.0 Hz, CHCH_3), 7.06 (1H, dd, J 5.0 and 7.5 Hz NCHCH), 7.45 (1H, d, J 7.5 Hz, CHCHCCH_3) and 8.35 (1H, d, J 3.5 Hz, NCH); δ_{C} (CDCl_3 , 125 MHz) 13.9 (q), 18.4 (q), 24.1 (q), 41.0 (d), 51.9 (q), 77.6 (s), 121.6 (d), 130.6 (s), 138.5 (d), 145.5 (d), 163.1 (s) and 177.6 (s); MS (CI^+) m/z 242 (MNH_4^+ , 10), 224 (MH^+ , 100), 221 (30), 208 (40) and 121 (30); HRMS (CI^+) calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_3$ (MH^+) 224.1287, found 224.1295 (δ = + 3.7 ppm).

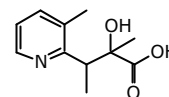
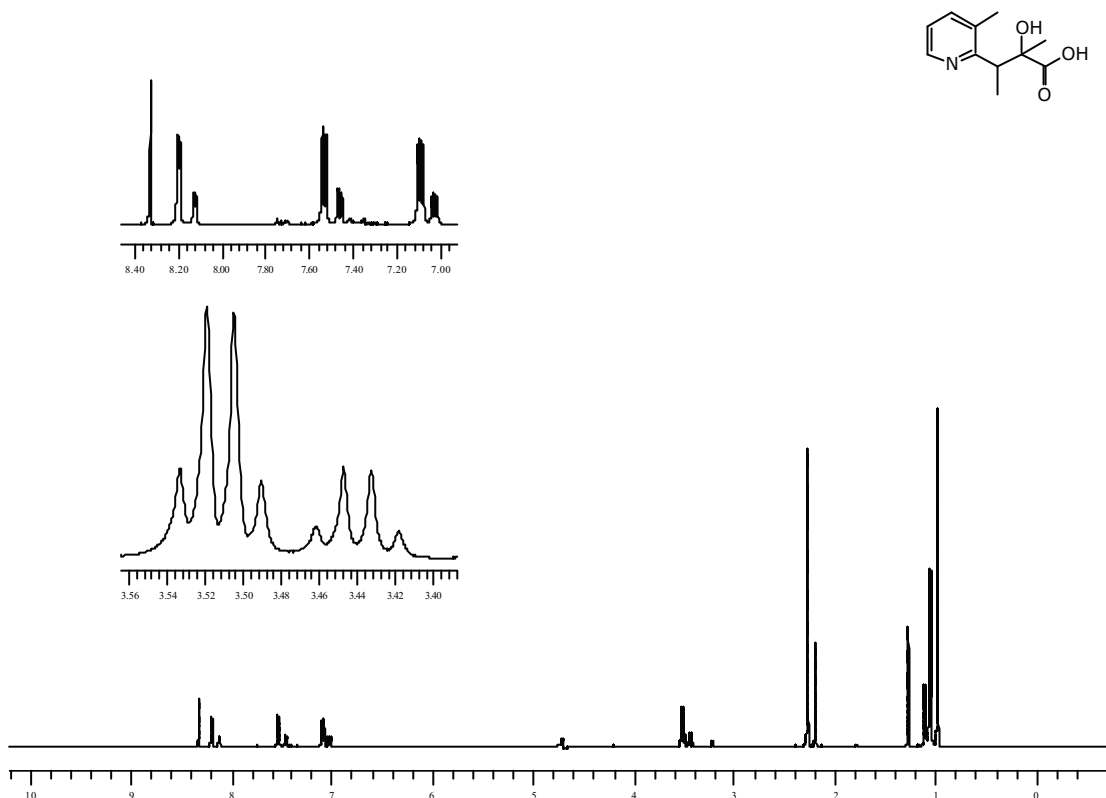


(±)-syn-2-Hydroxy-2-methyl-3-(3-methyl-pyridin-2-yl) butyric acid and (±)-anti-2-hydroxy-2-methyl-3-(3-methyl-pyridin-2-yl) butyric acid (177b and 177a).

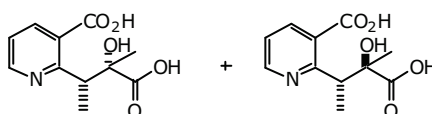


To a solution of α -hydroxy ester **176** (*dr* 75:25, **176a**:**176b**) (10 mg, 0.4 mmol) in methanol (500 μL) was added NaOH (2M, 100 μL) and the resultant solution was heated to reflux for 2 h. The reaction mixture was neutralised with 2M HCl (*ca.* 2 μL) and concentrated *in vacuo* to afford a white hygroscopic solid. Purification by reverse C18 FC (CH_3CN) afforded *acid* **177** (9 mg, 96%, *dr* 30:70, **177a**:**177b** by ^1H NMR) as a white hygroscopic solid. *R_f* 0.04 (EtOAc/ H_2O , 90:10); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3416, 2351, 1587 (C=O) and 1384; **Major**: δ_{H} (D_2O , 500 MHz) 0.98 (3H, s, CH_3COH), (3H, d, *J* 7.0 Hz, CH_3CH), 2.27 (3H, s, ArCH_3), 3.51 (1H, q, *J* 7.0 Hz, CHCH_3), 7.09 (1H, dd, *J* 5.5 and 8.0 Hz NCHCH), 7.53 (1H, d, *J* 8.0 Hz, NCHCHCH), 8.19 (1H, d, *J* 5.5 Hz, NCH) and 8.32 (1H, bs, OH); δ_{C} (D_2O , 125 MHz) 14.7 (q), 18.6 (q), 24.4 (q), 41.2 (d), 78.8 (s), 122.0 (d), 133.1 (s), 139.0 (d), 145.6 (d), 160.6 (s) and 182.6 (s); **Minor**: δ_{H} (D_2O , 500 MHz) 1.10 (3H, d, *J* 7.0 Hz, CH_3CH), 1.27 (3H, s, CH_3COH), 2.19 (3H, s, ArCH_3), 3.43 (1H,

q, J 7.0 Hz, CHCH₃), 7.03 (1H, dd, J 5.5 and 8.0 Hz NCHCH), 7.45 (1H, d, J 8.0 Hz, CHCHCCH₃), 8.13 (1H, d, J 5.5 Hz, NCH) and 8.32 (1H, bs, OH); δ_c (D₂O, 125 MHz) 13.4 (q), 17.8 (q), 22.8 (q), 40.8 (d), 78.7 (s), 121.9 (d), 131.02 (s), 145.3 (d), 162.7 (s), 171.0 (d) and 183.8 (s); MS (CI⁺) m/z 210 (MH⁺, 100); HRMS (CI⁺) calcd for C₁₁H₁₅NO₃ (MH⁺) 210.1130, found 210.1129 (δ = - 0.6 ppm).



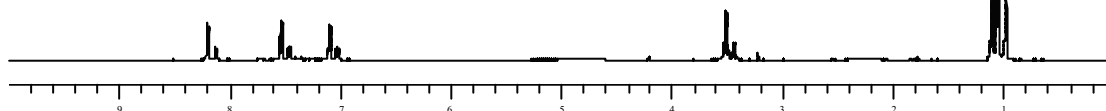
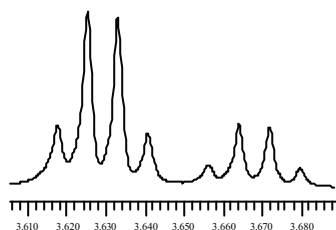
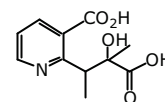
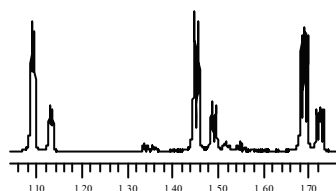
(±)-*syn*--2-(2-Carboxy-2-hydroxy-1-methylpropyl) nicotinic acid and (±)-*anti*-2-(2-carboxy-2-hydroxy-1-methylpropyl) nicotinic acid (**178b** and **178a**).



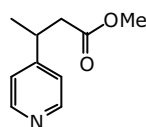
C₁₁H₁₃NO₅
Exact Mass: 239.08
Mol. Wt.: 239.22
C, 55.23; H, 5.48; N, 5.86; O, 33.44

To a mixture of α -hydroxy butyric acid **177** (*dr* 30:70, **177a**:**177b**) (10 mg, 0.05 mmol) and H₂O (500 μ L) was added KMnO₄ (31 mg, 0.12 mmol) and heated to reflux overnight. After filtration of precipitated MnO₂, the filtrate was concentrated to approx. 200 μ L. The resulting clear solution was acidified to *ca.* pH6 with 1N HCl. Purification by reverse phase C18 FC (CH₃CN) afforded *diacids* **178a** and **178b** (11 mg, 92%, *dr* 30:70, **178a**:**178b** by ¹H NMR) as a white hygroscopic solid. *R_f* 0.13 (CH₃CN/H₂O, 90:10); ν_{max} /cm⁻¹ (neat) 3582, 3416, 2351, 1666 (C=O) and 1650 (C=O); δ_H (D₂O, 500 MHz) 1.01 (3H, s, CH₃COH), 200

1.18 (3H, s, CH₃CH), 1.24 (3H, d, *J* 20.0 Hz, CH₃COH), 1.29 (3H, s, CH₃CH), 3.75-3.91 (1H, m, PyCH), 7.28-7.31 (1H, NCHCH), 7.71-7.74 (1H, NCHCHCH), 8.44 (1H, NCH); δ_c (D₂O, 125 MHz) 14.8 (q), 15.1 (q), 25.4 (q), 43.0 (d), 43.2 (d), 78.6 (s), 121.9 (d), 122.1 (d), 135.2 (d), 136.1 (d), 136.8 (s), 138.1 (d), 147.9 (d), 148.2 (d), 157.6 (s), 173.0 (s) and 177.0 (s); MS (CI⁺) *m/z* 239 (MH⁺, 30), 222 (50), 116 (60), 114 (100), 94 (30), 91 (80), 74 (40) and 52 (20); HRMS (CI⁺) calcd for C₁₁H₁₅N₂O₄ (MNH₄-H₂O)⁺ 239.1032, found 239.1032 (? = + 0.1 ppm).



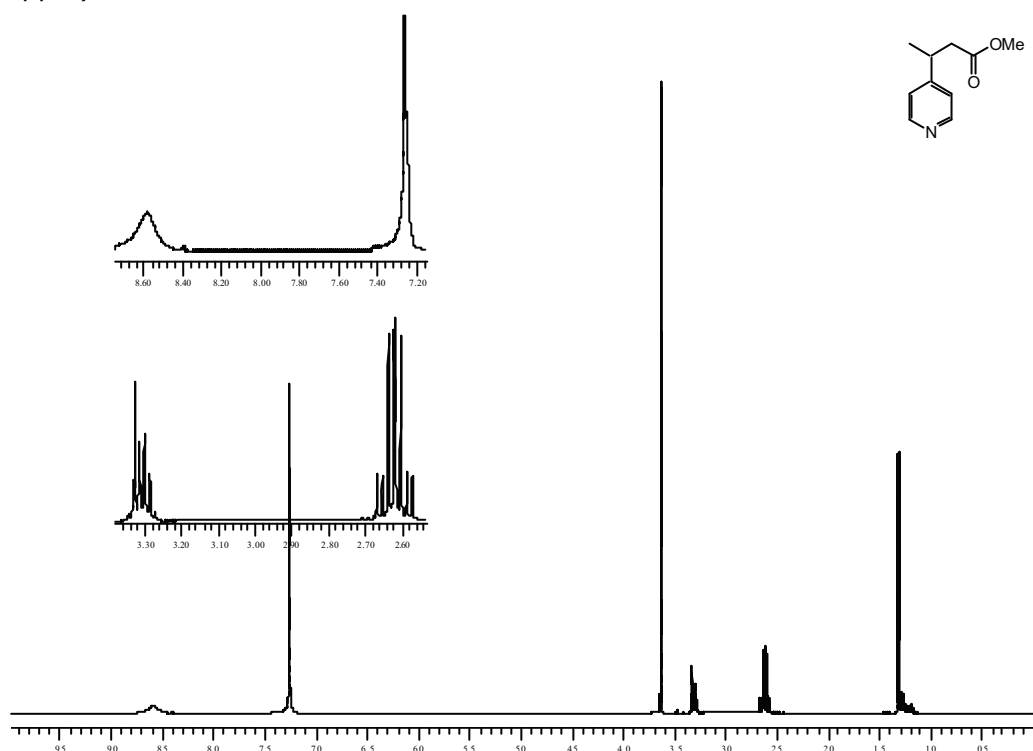
(±)-4-Pyridin-2-ylbutyric acid methyl ester, (180).



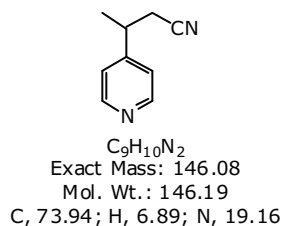
C₁₀H₁₃NO₂
 Exact Mass: 179.09
 Mol. Wt.: 179.22
 C, 67.02; H, 7.31; N, 7.82; O, 17.85

To a solution of 4-iodopyridine (300 mg, 1.5 mmol) in Et₂O (12.5 mL) at -78 °C was added a solution of *n*BuLi (2.30 M in hexanes, 636 μL, 1.5 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (105 mg, 0.7 mmol) in dibutylsulfide (255 μL, 1.5 mmol) and Et₂O (15 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of methyl crotonate (155 μL, 1.5 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (2 mL)

was added and the phases separated. The aqueous layer was extracted with Et₂O (3 × 30 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 30 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (nHexane/EtOAc, 50:50) afforded **ester 180** (204 mg, 78%) as a colourless oil. *R*_f 0.39 (nHexane/EtOAc, 50:50); $\nu_{\max}/\text{cm}^{-1}$ (neat) 3450, 2091, 1638 (C=O) and 1260; δ_{H} (CDCl₃, 500 MHz) 1.32 (3H, d, *J* 7.0 Hz, CH₃CH), 2.59 (1H, dd, *J* 7.0 and 16.0 Hz, CH₂), 2.64 (1H, dd, *J* 7.0 and 16.0 Hz, CH₂), 3.27-3.34 (1H, m, CH), 3.62 (3H, s, OCH₃), 7.26 (2H, bs, 2 × NCHCH) and 8.58 (2H, bs, 2 × NCH). δ_{C} (CDCl₃, 125 MHz) 21.1 (q), 35.9 (q), 41.5 (t), 51.7 (d), 100.0 (s), 148.6 (2d), 156.0 (2d), 171.9 (s); MS (CI⁺) *m/z* 180 (MH⁺, 80), 163 (50), 157 (20), 136 (100); HRMS (CI⁺) calcd for C₁₀H₁₄NO₂ (MH⁺) 180.1025, found 180.1029 (δ = + 0.4 ppm).

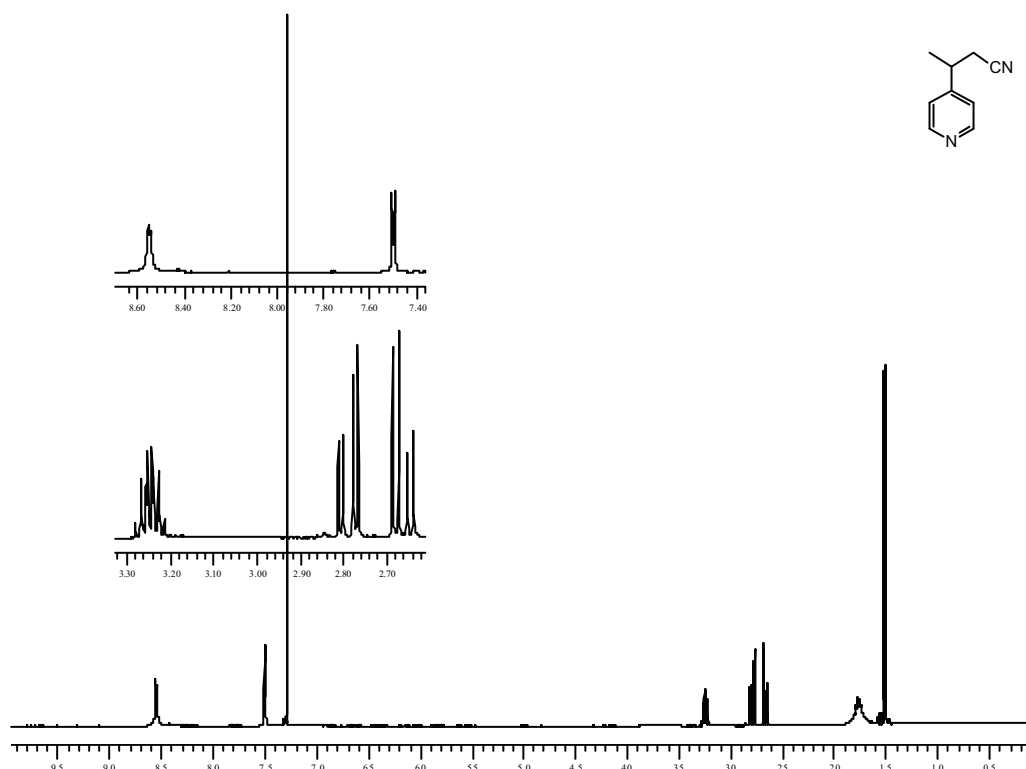


(±)-3-Pyridin-4-yl-butynitrile, (181).

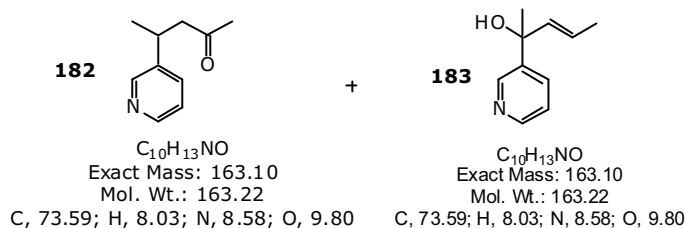


To a solution of 4-iodopyridine (300 mg, 1.5 mmol) in Et₂O (12.5 mL) at -78 °C was added a solution of *n*BuLi (2.30 M in hexanes, 636 μ L, 1.5 mmol) and the

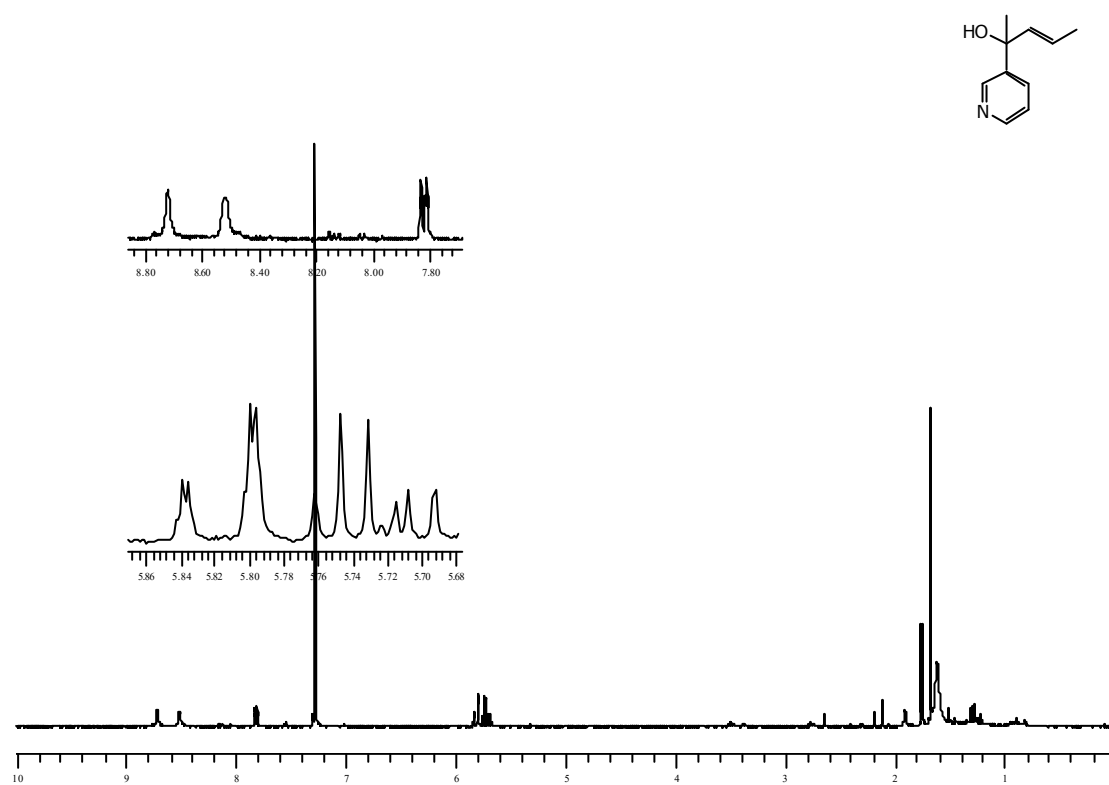
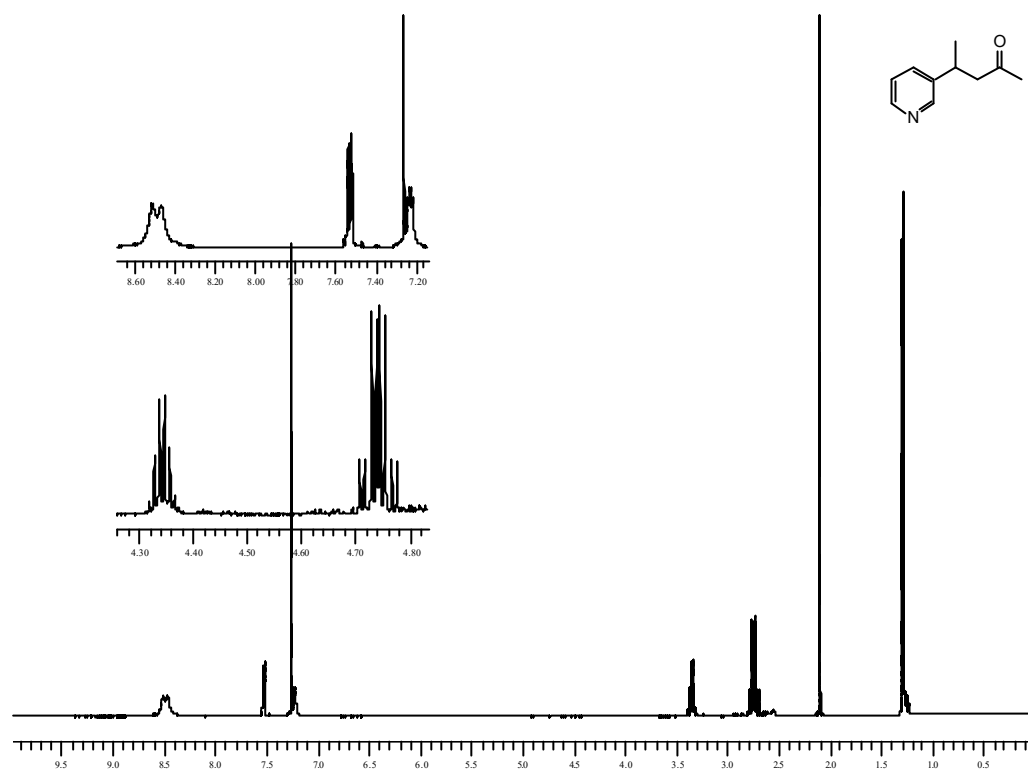
resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (105 mg, 0.7 mmol) in dibutylsulfide (255 μ L, 1.5 mmol) and Et₂O (15 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of crotononitrile (118 μ L, 1.5 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (2 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 $\times$ 30 mL). The organic extracts were combined and extracted with aqueous HCl (2 $\times$ 30 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 $\times$ 30 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (nHexane/EtOAc, 50:50) afforded ester **181** (98 mg, 90%) as a colourless oil. *R*_f 0.19 (nHexane/EtOAc, 50:50); ν_{max} /cm⁻¹ (neat) 3424, 2361, 1634, 1572 and 1063; δ_{H} (CDCl₃, 500 MHz) 1.51 (3H, d, *J* 7.0 Hz, CH₃CH), 2.66 (1H, dd, *J* 7.5 and 17.0 Hz, CH₂), 2.79 (1H, dd, *J* 7.5 and 17.0 Hz, CH₂), 3.22-3.27 (1H, m, CH), 7.49 (2H, d, *J* 5.5 Hz, 2 $\times$ NCHCH) and 8.54 (2H, d, *J* 5.5 Hz, 2 $\times$ NCH). δ_{C} (CDCl₃, 125 MHz) 19.4 (q), 24.8 (t), 42.2 (d), 120.4 (2d), 148.1 (s) and 150.0 (2d); MS (CI⁺) *m/z* 147 (MH⁺, 100); HRMS (CI⁺) calcd for C₉H₁₁N₂ (MH⁺) 147.1205, found 147.1204 (Δ = - 0.8 ppm).

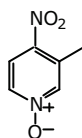


(±)-Pyridin-3-yl-pentan-2-one (182) and (±)-pyridin-3-yl-pent-3-en-2-ol (183).



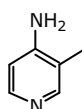
To a solution of *3-bromopyridine* (1.0 g, 6.0 mmol) in Et_2O (40 mL) at $-78\text{ }^{\circ}C$ was added a solution of $BuLi$ (2.1 M in hexanes, 2.9 mL, 6.0 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (571 mg, 3.0 mmol) in dibutylsulfide (1.0 mL, 6.0 mmol) and Et_2O (8 mL) at $0\text{ }^{\circ}C$. The resulting dark solution was stirred for 15 min at room temperature before addition of 3-penten-2-one (586 μL , 6.0 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (2 mL) was added and the phases separated. The aqueous layer was extracted with Et_2O ($3 \times 30\text{ mL}$). The organic extracts were combined and extracted with aqueous HCl ($2 \times 30\text{ mL}$, 2 M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et_2O ($3 \times 30\text{ mL}$). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC ($CHCl_3/Et_2O$, 3:1) afforded *ketone 182* (386 mg, 79%) as a colourless oil and *alcohol 183* (15 mg, 3%). as a colourless oil *Ketone 182*: R_f 0.30 ($CHCl_3/Et_2O$, 3:1); ν_{max}/cm^{-1} (neat) 3424, 2963, 2929, 1707 and 1638 (C=O); δ_H ($CDCl_3$, 500 MHz) 1.28 (3H, d, J 7.0 Hz, CH_3CH), 2.10 (3H, s, CH_3CO), 2.72 (1H, dd, J 7.5 and 17.0 Hz, CH_2), 2.77 (1H, dd, J 7.5 and 17.0 Hz, CH_2), 3.35 (1H, m, CH), 7.22-7.26 (1H, m, NCHCH), 7.53 (1H, dd, J 3.5 and 8.0 Hz, CHCHCH) and 8.50 (2H, bd, J 21.0 Hz, $2 \times NCH$); δ_C ($CDCl_3$, 100 MHz) 21.7 (q), 30.5 (d), 32.8 (t), 51.4 (q), 123.5 (d), 134.3 (d), 141.2 (s), 147.8 (d), 148.7 (d) and 206.9 (s); MS (CI^+) m/z 164 (MH^+ , 100); HRMS (CI^+) calcd for $C_{10}H_{14}NO$ (MH^+) 164.1075, found 164.1073 (δ = - 1.3 ppm). *Alcohol 183*: R_f 0.10 (EtOAc); ν_{max}/cm^{-1} (neat) 2930 (OH), 2954, 2361, 1419 and 970; δ_H ($CDCl_3$, 500 MHz) 1.62 (1H, bs, OH), 1.67 (3H, s, CH_3OH), 1.75 (3H, d, J 6.0 Hz CH_3CH), 5.69-5.83 (2H, $2 \times CH$), 7.29 (1H, bs, NCHCCCH), 7.82 (1H, d, J 6.0 Hz, NCHCH), 8.52 (1H, bs, NCHCC) and 8.72 (1H, bs, NCHCH); δ_C ($CDCl_3$, 125 MHz) 17.7 (q), 29.7 (q), 73.3 (s), 125.1 (2d), 133.0 (d), 137.3 (d), 147.3 (d), 148.0 (d) and 165.2 (s); MS (CI^+) m/z 164 (MH^+ , 100), 165 (30), 178 (NH_4^+ , 20); HRMS (CI^+) calcd for $C_{10}H_{14}NO$ (MH^+) 164.1075, found 164.1070 (δ = - 0.5 ppm).



3-Methyl-4-nitropyridine-*N*-oxide (185).¹⁸⁴

C₆H₆N₂O₃
 Exact Mass: 154.04
 Mol. Wt.: 154.12
 C, 46.76; H, 3.92; N, 18.18; O, 31.14

To a mixture of nitric acid (55 mL) and sulphuric acid (70 mL) at 0-5 °C was slowly added *3-picoline-1-oxide* (20 g, 0.2 mol). The resultant solution was heated slowly to 100-105 °C for 2 h. The cooled mixture was added to ice and sodium carbonate was added to between pH 2-3. Heavy crystallisation of *nitro-3-picoline-1-oxide* and sodium sulfate occurred. The mixture was left to stand overnight, the yellow solid was separated by filtration and washed with ice-water. The combined aqueous extracts were extracted with hot chloroform and the organics dried over Na₂SO₄ and concentrated *in vacuo* to give *N-oxide 185*. Purification by FC (CHCl₃) afforded *N-oxide 185* (25.7 g, 80%) as a pale crystalline solid. *R_f* 0.80 (CHCl₃/Et₂O, 9:1); mp: 135-136 °C (CHCl₃) [*cf.* lit,¹⁸⁴ 136-137 °C (CHCl₃)]. δ_H (CDCl₃, 270 MHz) 2.60 (3H, s, CH₃), 8.00 (1H, d, *J* 7.0 Hz, NCHCH), 8.10 (1H, d, *J* 7.0 Hz, NCHCH) and 8.11 (1H, s, NCHCH₃); MS (CI⁺) *m/z* 155 (MH⁺, 100), 139 (90), 156 (50), 172 (50); HRMS (CI⁺) calcd for C₆H₇N₂O₃ (MH⁺) 155.0457, found 155.0454 (? = + 1.8 ppm).

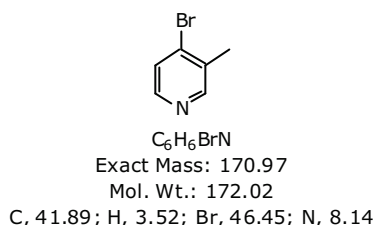
3-Methylpyridin-4-yl amine (186).¹⁸⁴

C₆H₈N₂
 Exact Mass: 108.07
 Mol. Wt.: 108.14
 C, 66.64; H, 7.46; N, 25.90

A mixture of *4-nitro-3-picoline-N-oxide* (1 g, 9.25 mmol) glacial acetic acid (30 mL) and iron powder (3 g, 53.6 mmol) was heated to 100 °C for 2 h. The reaction mixture was cooled to room temperature and the resulting mixture was diluted with H₂O (30 mL) and adjusted to pH 10-11 with NaOH (1M, 20 mL) and CHCl₃ (20 mL) was added and the precipitated iron hydroxide was filtered (CAUTION! keeping it continually covered with a layer of Et₂O). The collected solid was washed several times with Et₂O, and the combined organic extracts dried over Na₂SO₄ and concentrated *in vacuo* to give a white crystalline solid. Purification by recrystallisation from petroleum ether (60-80) afforded *amino 186* (378 mg, 54%) as a white crystalline solid. *R_f* 0.34 (CHCl₃/Et₂O, 9:1); mp: 107-109 °C (Et₂O) [*cf.* lit,¹⁸⁴ 108-109 °C (Et₂O)]. δ_H (CDCl₃, 270 MHz) 2.09 (3H, s, CH₃), 2.01

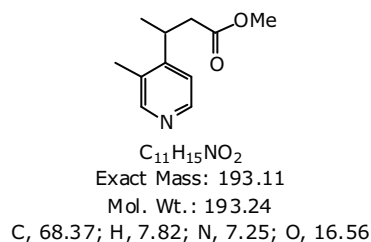
(2H, bs, NH₂), 6.46-6.49 (1H, m, NCHCH) and 8.08 (2H, NCH); MS (CI⁺) *m/z* 109 (MH⁺, 100), 110 (20), 108 (10); HRMS (CI⁺) calcd for C₆H₉N₂ (MH⁺) 109.0766, found 109.0766 (? = - 0.6 ppm).

4-Bromo-3-methylpyridine (**187**).¹⁷⁹



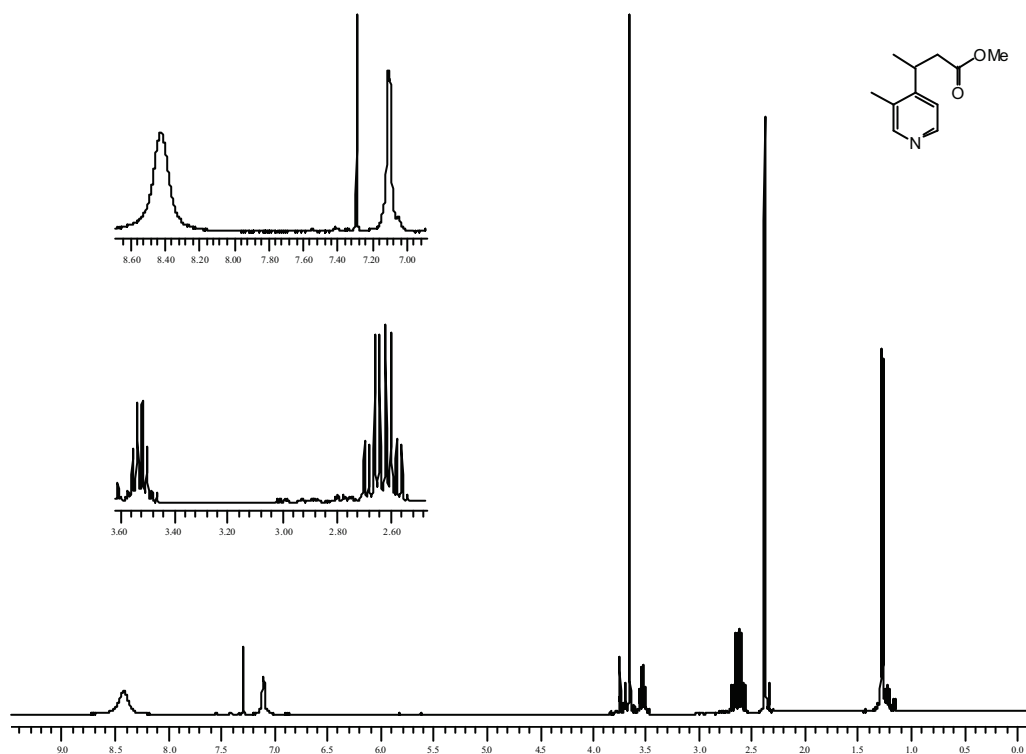
To a solution of *nitropyridine* **185** (2.50 g, 16.2 mmol) in EtOAc (150 mL) was added phosphorus tribromide (12.5 mL, 133.0 mmol). The resultant solution was stirred at ambient temperature for 10 min and then heated to reflux for 30 min. The reaction mixture was poured into ice (100 mL) and the pH adjusted to between 2 and 3 (NaOH pellets) and the solution extracted with EtOAc. The aqueous layer was made alkaline (pH 10), maintaining the temperature at 25-30 °C. The solution was then extracted into Et₂O (3 × 100 mL). The organic extracts were combined and dried over Na₂CO₃ and concentrated *in vacuo* to give bromopyridine **187** (2.22 g, 80%) as a red oil. *R_f* 0.15 (nHexane/EtOAc, 9:1); δ_H (CDCl₃, 400 MHz) 2.47 (3H, s, CH₃), 7.56 (1H, d, *J* 5.0 Hz, NCHCH), 8.31 (1H, d, *J* 5.0 Hz, NCHCH) and 8.51 (1H, s, NCH). MS (CI⁺) *m/z* 172 (MH⁺, 100), 174 (90), 94 (30) and 52 (80); HRMS (CI⁺) calcd for C₆H₇N⁷⁹Br (MH⁺) 171.9762, found 171.9757 (? = - 2.8 ppm).

(±)-(3-Methylpyridin-4-yl) butyric acid methyl ester (**189**).

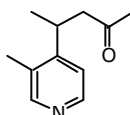


To a solution of 4-bromo-3-picoline (200 mg, 1.2 mmol) in Et₂O (10 mL) at -78 °C was added a solution of BuLi (2.3 M in hexanes, 504 μL, 1.2 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (100 mg, 0.6 mmol) in dibutylsulfide (203 μL, 1.2 mmol) and Et₂O (5 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of methyl crotonate (123 μL, 1.2 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (1 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O

(3 × 10 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 20 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (EtOAc/nHexane, 1:1) afforded ester **189** (72 mg, 65%) as a colourless oil. *R_f* 0.10 (EtOAc/nHexane, 1:1); ν_{max} /cm⁻¹ (neat) 3423, 2972, 2109, 1732 (C=O), 1638, 1436 and 1195; δ_{H} (CDCl₃, 400 MHz) 1.26 (3H, d, *J* 7.0 Hz, CH₃CH), 2.37 (3H, s, ArCH₃), 2.58 (1H, dd, *J* 8.0 and 15.5 Hz, CH₂), 2.65 (1H, dd, *J* 8.0 and 15.5 Hz, CH₂), 3.38-3.53 (1H, m, CH), 3.64 (3H, s, OCH₃), 7.09 (1H, bs, NCHCH) and 8.38 (2H, bs, NCH); δ_{C} (CDCl₃, 100 MHz) 16.1 (q), 20.7 (q), 31.1 (d), 40.9 (t), 51.7 (q), 121.1 (d), 120.2 (s), 147.9 (d), 151.0 (d), 152.7 (s) and 172.3 (s); MS (CI⁺) *m/z* 194 (MH⁺, 100), 150 (30), 94 (20); HRMS (CI⁺) calcd for C₁₁H₁₆NO₂ (MH⁺) 194.1181, found 194.1180 (Δ = - 0.5 ppm).



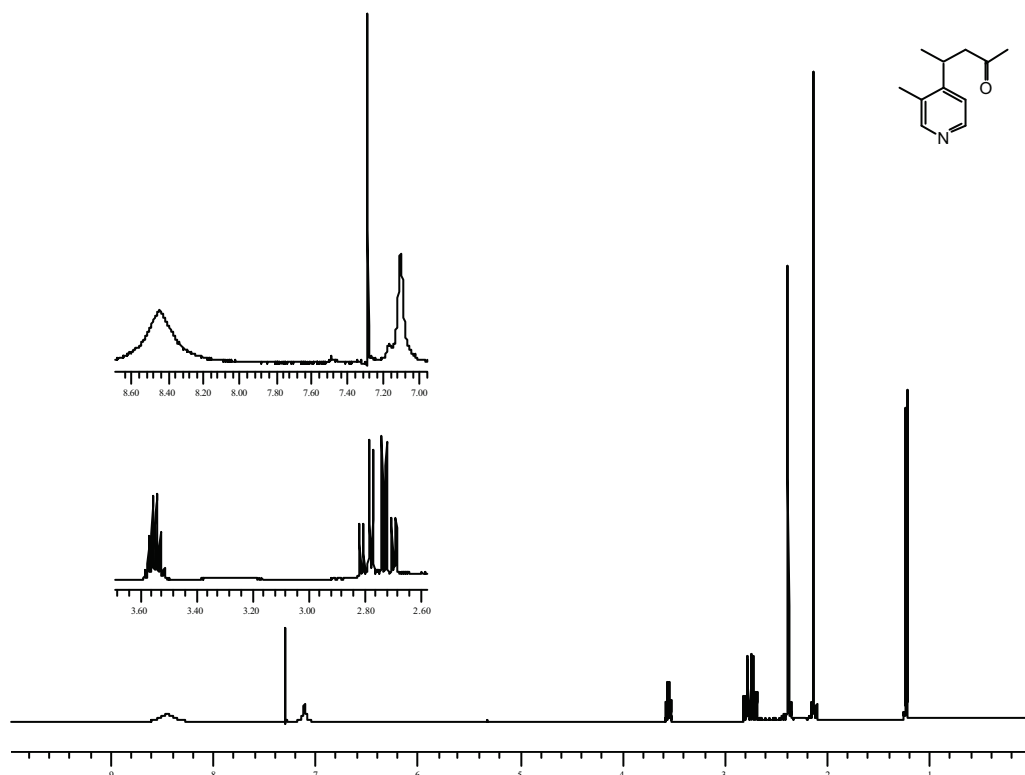
(±)-(3-Methylpyridin-4-yl) pentan-2-one (190).

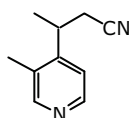


C₁₁H₁₅NO
 Exact Mass: 177.12
 Mol. Wt.: 177.24
 C, 74.54; H, 8.53; N, 7.90; O, 9.03

To a solution of 4-bromo-3-picoline (334 mg, 1.9 mmol) in Et₂O (12.5 mL) at -78 °C was added a solution of BuLi (1.8 M in hexanes, 843 μ L, 1.9 mmol) and the

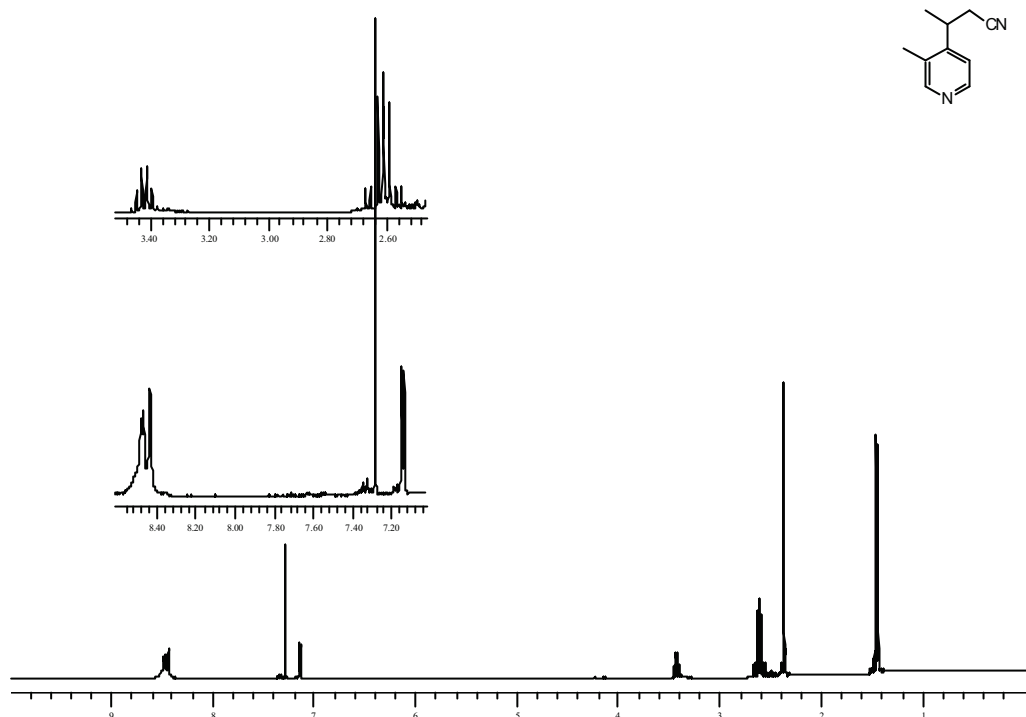
resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (185 mg, 1.0 mmol) in dibutylsulfide (339 μ L, 1.9 mmol) and Et₂O (8.5 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of 3-penten-2-one (189 μ L, 1.9 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (1 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 $\times$ 10 mL). The organic extracts were combined and extracted with aqueous HCl (2 $\times$ 20 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 $\times$ 10 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (EtOAc/nHexane, 1:1) afforded **ketone 190** (141 mg, 82%) as a colourless oil. *R*_f 0.28 (EtOAc); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3418, 2073, 1708, 1636 (C=O), 1406, 1361 and 1067; δ_{H} (CDCl₃, 400 MHz) 1.21 (3H, d, *J* 7.0 Hz, CH₃CH), 2.12 (3H, s, ArCH₃), 2.37 (3H, s, COCH₃), 2.69 (1H, dd, *J* 7.5 and 17.0 Hz, CH₂), 2.73 (1H, dd, *J* 7.5 and 17.0 Hz, CH₂), 3.52-3.57 (1H, m, CH), 7.07 (1H, bs, NCHCH) and 8.40 (2H, bs, 2 $\times$ NCH); δ_{C} (CDCl₃, 100 MHz) 16.2 (q), 20.7 (q), 29.9 (d), 30.5 (q), 50.2 (t), 147.8 (d), 151.1 (d), 151.5 (s), 153.1 (d), 153.1 (s) and 205.8 (s); MS (CI⁺) *m/z* 178 (MH⁺, 100), 169 (10); HRMS (CI⁺) calcd for C₁₁H₁₆NO (MH⁺) 178.1231, found 178.1232 (δ = - 0.4 ppm).



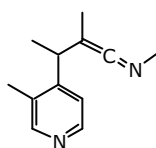
(±)-3-(3-Methylpyridin-4-yl) butyronitrile (191).

C₁₀H₁₂N₂
 Exact Mass: 160.10
 Mol. Wt.: 160.22
 C, 74.97; H, 7.55; N, 17.48

To a solution of 4-bromo-3-picoline (200 mg, 1.2 mmol) in Et₂O (10 mL) at -78 °C was added a solution of BuLi (2.3 M in hexanes, 504 µL, 1.2 mmol) and the resulting deep-red solution was stirred for 30 min before cannulation into a solution of copper(I) iodide (100 mg, 0.6 mmol) in dibutylsulfide (203 µL, 1.2 mmol) and Et₂O (5 mL) at 0 °C. The resulting dark solution was stirred for 15 min at room temperature before addition of crotononitrile (94 µL, 1.2 mmol). After stirring for 1 h at room temperature saturated aqueous ammonia (1 mL) was added and the phases separated. The aqueous layer was extracted with Et₂O (3 × 10 mL). The organic extracts were combined and extracted with aqueous HCl (2 × 20 mL, 2M). The combined aqueous extracts were made basic by addition of saturated aqueous ammonia and re-extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow oil. Purification by FC (EtOAc/nHexane, 1:1) afforded nitrile **191** (64 mg, 69%) as a colourless oil. *R_f* 0.29 (EtOAc); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3420, 2973, 2245, 2188, 1636, 1596, 1558, 1455, 1405, 1387 and 1197; δ_{H} (CDCl₃, 400 MHz) 1.44 (3H, d, *J* 7.0 Hz, CH₃CH), 2.37 (3H, s, ArCH₃), 2.60 (1H, dd, *J* 6.5 and 17.0 Hz, CH₂), 2.63 (1H, dd, *J* 6.5 and 17.0 Hz, CH₂), 3.40-3.45 (1H, m, CH), 7.14 (1H, d, *J* 5.0 Hz NCHCH), 8.43 (1H, s, NCH) and 8.47 (1H, d, *J* 5.0 Hz, NCH); δ_{C} (CDCl₃, 100 MHz) 16.1 (q), 19.8 (q), 24.5 (t), 31.5 (d), 117.9 (s), 119.6 (d), 130.6 (s), 148.4 (d), 149.8 (s) and 151.5 (s); MS (CI⁺) *m/z* 161 (MH⁺, 100); HRMS (CI⁺) calcd for C₁₀H₁₃N₂ (MH⁺) 161.1079, found 161.1072 (δ = - 3.9 ppm).

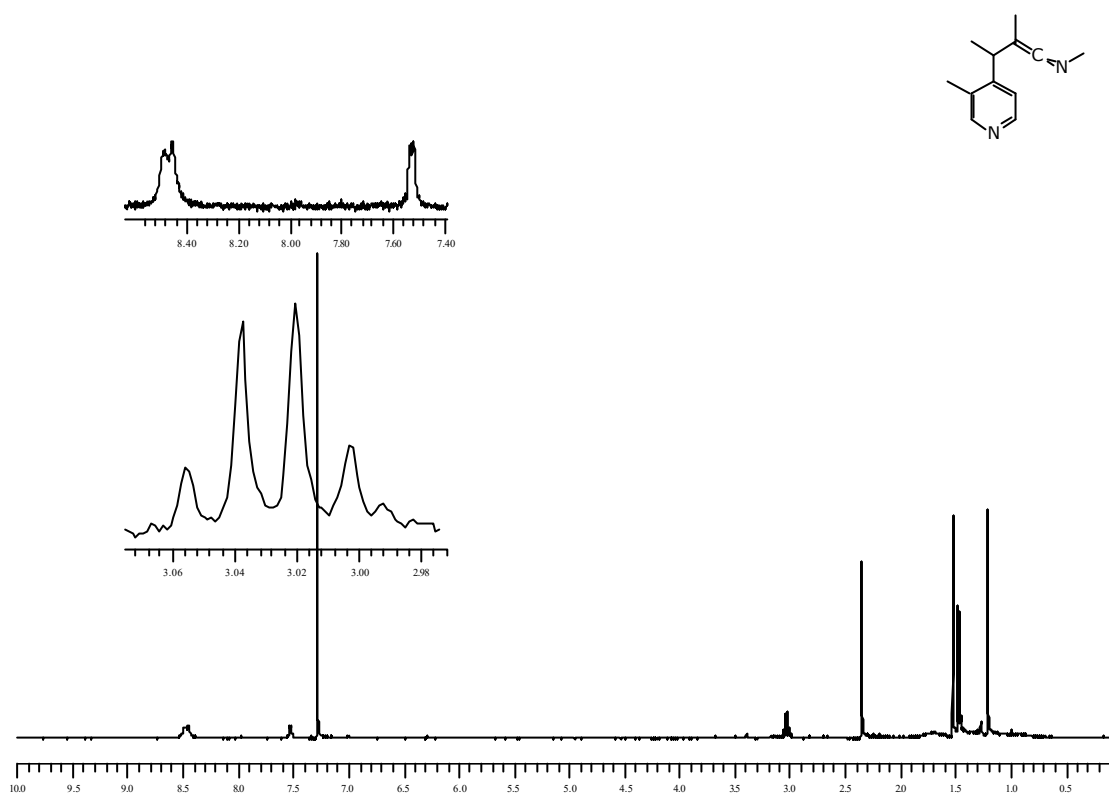


(±)-Methyl-[2-methyl-3-(3-methylpyridin-4-yl)-but-1-enylidene] amine (193)



C₁₂H₁₆N₂
 Exact Mass: 188.13
 Mol. Wt.: 188.27
 C, 76.55; H, 8.57; N, 14.88

To a solution of KHMDS (0.5 M in toluene, 138 μ L, 0.07 mmol) at -78 $^{\circ}$ C was added a solution of *nitrile* **191** (10 mg, 0.06 mmol) in toluene (50 μ L). The reaction mixture was stirred at -78 $^{\circ}$ C for 1 h and then a solution of MeI (3.5 μ L, 0.07 mmol) in toluene (50 μ L) was added dropwise. The reaction mixture was left to stir for 36 h at -78 $^{\circ}$ C, after which time the reaction mixture was quenched with saturated aqueous NH₄Cl (100 μ L). The resulting mixture was diluted with H₂O (200 μ L) and extracted with Et₂O (3 $\times$ 100 μ L). The combined organic extracts were washed with brine (200 μ L), dried over MgSO₄ and concentrated *in vacuo* to give *iminoketene* **193** (3 mg, 27%) as a colourless oil. *R*_f 0.34 (CHCl₃/Et₂O, 50:50); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3424, 2089, 1641 (C=O) and 1080; δ_{H} (CDCl₃, 400 MHz) 1.21 (3H, s, CH₃C=C), 1.47 (3H, d, *J* 7.0 Hz, CH₃CH), 1.53 (3H, s, NCH₃), 3.00-3.03 (1H, ArCHCH₃), 7.53 (1H, d, *J* 4.5 Hz, NCHCH) and 8.45-8.48 (2H, m, NCH); MS (CI⁺) *m/z* 208 (MH⁺, 20), 194 (100), 180 (20), 102 (90), 86 (10); HRMS (CI⁺) calcd for C₁₂H₁₈NO₂ (MH⁺) 208.1338, found 208.1323 (δ = -1.5 ppm).



7 Appendices

Appendix 1: Purification of Solvents.

All solvents were distilled before use. Petrol refers to the fraction of light petroleum-ether boiling between 40-60°C. Anhydrous solvents and reagents were obtained as follows:

CH₂Cl₂	distilled from CaH ₂ under argon immediately prior to use.
DME	stirred over CaH ₂ under argon for 24 h, distilled under a reduced pressure of argon, and stored over molecular sieves (4Å) under argon.
DMF	stirred over CaH ₂ under argon for 24 h, filtered, and distilled under a reduced pressure of argon from grade 1 (basic) alumina and stored over molecular sieves (4Å) under argon.
Et₂O	distilled from sodium/benzophenone ketyl under argon immediately prior to use.
EtOH	distilled from magnesium ethoxide and stored under argon.
HMPA	stirred over CaH ₂ under argon for 24 h, distilled under reduced pressure, and stored over molecular sieves (4Å) under argon.
MeOH	distilled from magnesium methoxide and stored under argon.
Pyridine	distilled from calcium hydride and stored under argon.
THF	distilled from sodium/benzophenone ketyl under argon immediately prior to use.
Toluene	stirred over CaH ₂ under argon for 24 h, distilled under a reduced pressure of argon, and stored over molecular sieves (4Å) under argon.
Dioxane	distilled from sodium/benzophenone ketyl under argon immediately prior to use.

Appendix 2: Purification of Reagents.

All chemicals were handled in accordance with COSHH regulations. All reagents were used as commercially supplied unless specified otherwise below:

***n*-Butyl lithium**

Solutions of butyl lithium were used as supplied by *Acros* and titrated with diphenylacetic acid immediately prior to use

***sec*-Buthyl lithium**

Solutions of butyl lithium were used as supplied by *Acros* and titrated with diphenylacetic acid immediately prior to use

***tert*-Butyl Lithium**

Solutions of butyl lithium were used as supplied by *Acros* and titrated with diphenylacetic acid immediately prior to use

***N,N,N',N'*-Tetramethylethylenediamine (TMEDA)**

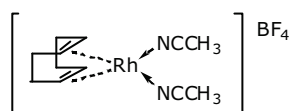
Solutions of TMEDA were distilled from *n*-BuLi immediately prior to use. The fraction boiling at 120-122°C at 1 atm was collected.

Lithium fluoride

Lithium fluoride was used as supplied from *Aldrich* but placed in a vacuum desiccator for 24 hours prior to use.

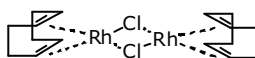
Triethylamine

Triethylamine was purified by distillation over calcium hydride. The fraction boiling at 76°C was collected.

Appendix 3: Preparation of Rhodium Catalysts**[Rh(cod)(MeCN)₂]BF₄.¹⁸⁵**

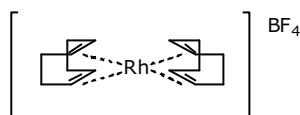
C₁₂H₁₈BF₄N₂Rh
Mol. Wt.: 378.8

[Rh(cod)₂]BF₄·xH₂O (50 mg, 0.12 mmol) was dissolved in MeCN (4 mL). Et₂O (5 mL) was added dropwise. The resultant yellow precipitate was dried over MgSO₄, filtered and concentrated *in vacuo* to afford the *title rhodium complex* (36 mg, 77%) as a yellow powder. mp: 186-189 °C (Et₂O) [lit, 188-190 °C]¹⁸⁵; $\nu_{\max}$ cm⁻¹ (neat) 2320 (CN), 2290 (CN), 1060 (BF₄) and 1030 (BF₄); δ_{H} (CDCl₃, 300 MHz) 1.90 (4H, broad d, *J* 8.0, equatorial CH), 2.37 (6H, s, CH₃), 3.50 (4H, broad s, axial CH) and 4.41 (4H, broad s, C=CH).

[RhCl(COD)]₂.¹⁸⁶

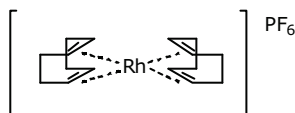
C₁₆H₂₄Cl₂Rh₂
Exact Mass:
Mol. Wt.: 493.08
C, 38.97; H, 4.91; Cl, 14.38; Rh, 41.74

To a solution of RhCl₃·3H₂O (2.00 g, 9.56 mmol) and 1,5-cyclooctadiene (6 mL, 49 mmol) in ethanol (30 mL) and water (3 mL) was heated to reflux for 18 hours. The cooled suspension was filtered and the solid washed with ethanol and dried *in vacuo* to afford the *title rhodium complex* (1.50 g, 62%) as a yellow microcrystalline solid. mp: 100-102 °C (Et₂O); δ_{H} (DMSO, 500 MHz) 1.97 (8H, d, *J* 8.0, axial CH), 2.41 (8H, m, equatorial CH) and 4.43 (8H, broad s, C=CH); δ_{C} (DMSO, 500 MHz) 30.07(t), 87.14(d).

[Rh(cod)₂]BF₄.¹⁸⁵

C₁₆H₂₄BF₄Rh
 Exact Mass:
 Mol. Wt.: 406.07
 C, 47.32; H, 5.96; B, 2.66; F, 18.71; Rh, 25.34

To a solution of [RhCl(cod)]₂ (500 mg, 1.01 mmol) in CH₂Cl₂ (10 mL) was added 1,5-cyclooctadiene (373 μL, 3.04 mmol) followed by AgBF₄ (434.1 mg, 2.23 mmol). This resulted in the immediate formation of a deep red solution, containing a white precipitate which was stirred for 30 mins and then filtered through a small pad of celite® which was washed with CH₂Cl₂ until the filtrate ran clear. The filtrate was reduced in volume (ca 20 mL) and then THF (10 mL) was added. The remaining solvent was subsequently removed *in vacuo* to give a red solid. The remaining solid was washed with THF (10 mL) followed by pentane (10 mL) and dried with MgSO₄ to afford the *title rhodium complex* (634 mg, 77%) as a red microcrystalline solid. mp: 207-209 °C (Et₂O) (lit, 206-208 °C)¹⁸⁵; ν_{max}/cm⁻¹ (KBr) 1060 (BF₄) and 1030 (BF₄); δ_H (CDCl₃, 300 MHz) 2.52 (16H, m, CH₂) and 5.37 (8H, broad s, C=CH); δ_F (DMSO, 250 MHz) -69.61 (6F, wide d, *J* 756.0).

[Rh(COD)₂]PF₆.¹⁸⁷

C₁₆H₂₄F₆PRh
 Exact Mass:
 Mol. Wt.: 464.23
 C, 41.40; H, 5.21; F, 24.55; P, 6.67; Rh, 22.17

To a solution of [RhCl(cod)]₂ (500 mg, 1.01 mmol) in CH₂Cl₂ (10 mL) was added 1,5-cyclooctadiene (373 μL, 3.04 mmol) followed by AgPF₆ (564 mg, 2.23 mmol). This resulted in the immediate formation of a deep red solution, containing a white precipitate which was stirred for 30 mins and then filtered through a small pad of celite® which was washed with CH₂Cl₂ until the filtrate ran clear. The filtrate was reduced in volume (ca 20 mL) and then THF (10 mL) was added. The remaining solvent was subsequently removed *in vacuo* to give a red solid. The remaining solid was washed with THF (10 mL) followed by pentane (10 mL) and dried with MgSO₄ to afford the *title rhodium complex* (535 mg, 57%) as a red microcrystalline solid. mp: 210-212 °C (Et₂O); ν_{max}/cm⁻¹ (KBr) 1081 (PF₆) and 1039 (PF₆); δ_H (DMSO, 500 MHz) 1.71 (8H, d, *J* 8.0, equatorial CH) 3.99 (8H, broad s, axial CH) and 5.49 (8H, broad s, C=CH). δ_F (DMSO, 250 MHz) -69.61 (6F, broad d, *J* 711.5); δ_C (DMSO, 250 MHz) 27.0 (t), 29.8 (t) and 128.4 (d).

8 References

- (1). Duan, H.; Takaishi, Y. *Phytochemistry* **1998**, 49, 2185.
- (2). Spivey, A. C.; Weston, M.; Woodhead, S. *Chem. Soc. Rev.* **2002**, 31, 43.
- (3). Duan, H.; Takaishi, Y.; Bando, M.; Kido, M.; Imakura, Y.; Lee, K. *Tetrahedron Lett.* **1999**, 40, 2969.
- (4). Duan, H.; Takaishi, Y.; Imakura, Y.; Jia, Y.; Li, D.; Cosentino, L. M.; Lee, K.-H. *J. Nat. Prod.* **2000**, 63, 357.
- (5). Luftmann, H.; Spiteller, G. *Tetrahedron* **1974**, 30, 2577.
- (6). Pailer, M.; Streicher, W. *Monatsh. Chem.* **1971**, 102, 1873.
- (7). Robert, L.; Baxter, W.; Crombie, L. M.; Crombie, L.; Simmonds, D. J.; Whiting, D. A. *J. Chem. Soc., Perkin Trans I* **1979**, 12, 2982.
- (8). Taylor, I. F.; Watson, W. H. *Acta. Cryst.* **1977**, B33, 3176.
- (9). White, J. D.; Shin, H.; Kim, T.-S.; Cutshall, N. S. *J. Am. Chem. Soc.* **1997**, 119, 2404.
- (10). Crombie, L.; Crombie, W. M. L.; Whiting, D. A. *The Alkaloids* **1990**, 39, 139.
- (11). Spivey, A. C.; Woodhead, S. J.; Weston, M.; Andrews, B. I. *Angew. Chem. Int. Ed.* **2001**, 40, 769.
- (12). Libiseller, R.; Preisinger, A. *Monatsh. Chem.* **1962**, 93, 17.
- (13). Pailer, M.; Libiseller, R. *Monatsh. Chem.* **1962**, 93, 403.
- (14). Pailer, M.; Libiseller, R. *Monatsh. Chem.* **1962**, 93, 511.
- (15). Smith, R. M. *The Alkaloids* **1977**, 16, 215.
- (16). Klasek, A.; Santavy, F.; Duffield, A. M.; Reichstein, T. *Helv. Chim. Acta.* **1971**, 54, 2144.
- (17). Shizuri, Y.; Wada, H.; Sugiura, K.; Yamada, K.; Hirata, Y. *Tetrahedron* **1973**, 29, 1773.
- (18). Kuo, Y. H.; Chen, C. H.; Chen, C. F.; King, M. L.; Chen, H. Y.; Chen, K.; Lee, K. H. *J. Nat. Prod.* **1994**, 57, 263.
- (19). Whiting, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2313.
- (20). Beroza, M. *J. Am. Chem. Soc.* **1953**, 75, 44.
- (21). Yamada, K.; Shizuri, Y.; Hirata, Y. *Tetrahedron* **1978**, 34, 1915.
- (22). Pailer, M.; Pfleger, K. *Monatsh. Chem.* **1976**, 107, 965.
- (23). Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis.*; 1st ed.; Pergamon Press, Oxford, **1992**.
- (24). Komnenos, T. *Leibigs Ann. Chem.* **1883**, 218, 145.
- (25). Michael, A. *J. Prakt. Chem.* **1887**, 3, 349.
- (26). Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, 10, 179.
- (27). Brimble, M. A.; Nairn, M. R.; Prabakaran, H. *Tetrahedron* **2000**, 56, 1937.

- (28). Jankowski, P.; Marczak, S.; Wicha, J. *Tetrahedron* **1998**, *54*, 12071.
- (29). Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.
- (30). Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.
- (31). Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
- (32). Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393.
- (33). Nakamura, E.; Mori, S. *Angew. Chem. int. Ed.* **2000**, *39*, 3750.
- (34). Krause, N.; Gerold, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186.
- (35). Harutyunyan, R. S.; Lopez, F.; Browne, W. R.; Correa, A.; Pena, D.; Badorrey, R.; Meetsma, A.; Minnaard, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103.
- (36). Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141.
- (37). Frantz, D. E.; Singleton, D. A.; Synder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383.
- (38). Mori, S.; Uerdingen, M.; Krause, N.; Morokuma, K. *Angew. Chem. int. Ed.* **2005**, *44*, 4715.
- (39). Bertz, S. H.; Carlin, M. K.; Deadwyler, D. A.; Murphy, M.; Olge, C. A.; Seagle, P. H. A. *J. Am. Chem. Soc.* **2002**, *124*, 13650.
- (40). Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 1826.
- (41). Corey, E. J.; Boaz, N. *Tetrahedron Lett.* **1985**, *26*, 6015.
- (42). Murphy, M. D.; Ogle, G.; Bertz, S. H. *Chem. Commun.* **2005**, 854.
- (43). Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11025.
- (44). Yamanaka, M.; Nakamura, E. *Organometallics* **2001**, *20*, 5675.
- (45). Taylor, R. J. K. *Organocopper Reagents A Practical Approach*; 1st ed.; Oxford University Press: New York, **1994**.
- (46). Kauffmann, T. *Angew. Chem.* **1974**, *86*, 321.
- (47). Parks, E.; Wagner, B. E.; Holm, R. H. *J. Organomet. Chem.* **1973**, *56*, 53.
- (48). Malmberg, H.; Nilsson, M. *Tetrahedron* **1982**, *38*, 1509.
- (49). Malmberg, H.; Nilsson, M. *J. Organomet. Chem.* **1983**, *243*, 241.
- (50). Malmberg, H.; Nilsson, M. *Tetrahedron* **1986**, *42*, 3981.
- (51). Caprio, V.; Mann, J. J. *J. Chem. Soc., Perkin Trans 1* **1998**, 3151.
- (52). Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 3291.
- (53). Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *20*, 7210.
- (54). House, H. O.; Fisher, W. F. *J. Org. Chem.* **1969**, *34*, 3615.
- (55). Houpis, I. N.; Lee, J. *Tetrahedron* **2000**, *56*, 817.
- (56). Ashby, E. C.; Heinsohn, G. *J. Org. Chem.* **1974**, *39*, 3297.
- (57). Petrier, C.; Barbosa, J. *J. Org. Chem.* **1985**, *50*, 5761.
- (58). Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931.

- (59). Dayrit, F. M.; Gladkowski, D. E.; Schwartz, J. J. *Am. Chem. Soc.* **1981**, *103*, 4466.
- (60). Cacchi, S.; Palmieri, G. *J. Organomet. Chem.* **1985**, *282*, C3.
- (61). Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175.
- (62). Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4148.
- (63). Ahn, K.-H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178.
- (64). Bolm, C. *Tetrahedron Asym.* **1991**, *2*, 701.
- (65). Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron; Asymmetry*. **1992**, *3*, 581.
- (66). Corma, A.; Iglesias, M.; M, V. M.; Rubio, J.; Sanchez, F. *Tetrahedron Asym.* **1992**, *3*, 845.
- (67). Soai, K.; Hayasaka, T.; Ugajin, S. *Chem. Commun.* **1989**, 516.
- (68). Uemura, M.; Miyake, R.; Nakayama, K.; Shiro, M.; Hayashi, Y. *J. Org. Chem.* **1993**, *58*, 1238.
- (69). Lambert, F.; Knotter, D. M.; Janssen, M. D.; Klaveren, M. v.; Boersma, J.; Koten, B. v. *Tetrahedron; Asymmetry*. **1991**, *2*, 1097.
- (70). Spescha, M. *Helv. Chim. Acta.* **1993**, *76*, 1219.
- (71). Zhou, O.-L.; Pfaltz, A. *Tetrahedron Lett.* **1993**, *34*, 7725.
- (72). Tanaka, K.; Matsui, J.; Suzuki, H. *J. Chem. Soc. Perkin Trans 1* **1993**, 153.
- (73). Knotter, D. M.; Koten, G. v.; Maanen, H. L. v.; Grove, D. M.; Spek, A. L. *Angew. Chem. Int. Ed.* **1989**, *28*, 341.
- (74). Klaveren, M. v.; Lambert, F.; Eijkelkamp, D. J. F. M.; Grove, D. M.; Koten, G. v. *Tetrahedron Lett.* **1994**, *35*, 6135.
- (75). Zhou, Q.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467.
- (76). Knobel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429.
- (77). Stangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503.
- (78). Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. *Tetrahedron; Asymmetry*. **1997**, *8*, 3987.
- (79). Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, P. *Tetrahedron; Asymmetry*. **1997**, *8*, 3193.
- (80). Alexakis, A.; Burton, V. J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869.
- (81). Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275.
- (82). Nakagawa, Y.; Kanai, M.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1996**, *37*, 7805.

- (83). Seebach, D.; Jaeschke, G.; Pichota, A.; Audergon, L. *Helv. Chim. Acta.* **1997**, *80*, 2515.
- (84). Varies, A. H. M. d.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 2374.
- (85). Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784.
- (86). Feringa, B. L.; Badorrey, R.; Pena, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5834.
- (87). Lopez, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 2752.
- (88). Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.
- (89). Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.
- (90). Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579.
- (91). Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951.
- (92). Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.
- (93). Hayashi, T.; Takashiaki, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.
- (94). Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 12102.
- (95). Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667.
- (96). Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97.
- (97). Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91.
- (98). Hayashi, T. *Synlett* **2001**, 879.
- (99). Pucheault, M.; Darses, S.; Genet, J.-P. *Tetrahedron Lett.* **2002**, *43*, 6155.
- (100). Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.
- (101). Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508.
- (102). Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873.
- (103). Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 781.
- (104). Batey, R. A.; Thadaru, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683.
- (105). Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J. A. F.; de Varies, A. H. M.; de Varies, J. G.; Minnaard, A.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045.

- (106). Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem. Int. Ed.* **2004**, *43*, 719.
- (107). Oppolzer, W.; Barras, J.-P. *Helv. Chim. Acta.* **1987**, *70*, 1666.
- (108). Oppolzer, W.; Dudfield, P. *Helv. Chim. Acta.* **1985**, *68*, 216.
- (109). Oppolzer, W.; Loher, H. J. *Helv. Chim. Acta.* **1981**, *64*, 2808.
- (110). Oppolzer, W.; Mills, R. J.; Pachinger, W.; Stevenson, T. *Helv. Chim. Acta.* **1986**, *69*, 1542.
- (111). Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.
- (112). Pena, D.; Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1836.
- (113). Donohoe, T. J.; Mace, L.; Helliwell, M.; Ichihara, O. *Synlett* **2002**, *2*, 331.
- (114). Vollhardt, K. P. C. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539.
- (115). Coudret, C. *Synth. Commun.* **1996**, *26*, 3543.
- (116). Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369.
- (117). Darses, S.; Genet, J. P. *Eur. J. Org. Chem.* **2003**, 4313.
- (118). Oi, S.; Moro, M.; Inoue, Y. *Chem. Commun.* **1997**, 1621.
- (119). Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Queguiner, G.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 292.
- (120). Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.
- (121). Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.
- (122). Farina, V. *J. Org. Chem.* **1991**, *56*, 4985.
- (123). Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *J. Org. Chem.* **1994**, *59*, 7259.
- (124). Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200.
- (125). Renaud, P.; Lacote, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123.
- (126). Phillips, J. E.; Herber, R. H. *J. Organomet. Chem.* **1984**, *268*, 39.
- (127). Katritzky, A. R.; Watson, C. H.; Degaszafran, Z.; Eyler, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 2471.
- (128). Millner, O. E.; Stanley, J. W.; Purcell, W. P. *J. Med. Chem.* **1974**, *17*, 13.
- (129). Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.
- (130). Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935.
- (131). Broxton, T. J.; Chung, R. P. T. *J. Org. Chem.* **1986**, *51*, 3112.
- (132). Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
- (133). Spivey, A. C.; Turner, D. J.; Turner, M. L.; Yeates, S. *Org. Lett.* **2002**, *4*, 1899.
- (134). Mongin, F.; Trecourt, F.; Mongin, O.; Queguiner, G. *Tetrahedron* **2002**, *58*, 309.

- (135). Katritzky, A. R. *Adv. Heterocyclic Chem.* **1991**, 52, 240.
- (136). Collum, D. B. *Acc. Chem. Res.* **1992**, 25, 448.
- (137). Marsais, F.; Nard, G. L.; Queguiner, G. *Synthesis* **1982**, 235.
- (138). Queguiner, G. *Adv. Heterocyclic Chem.* **1991**, 52, 244.
- (139). Oi, S.; Moro, M.; Fukuhara, H.; Kawanishi, T.; Inoue, Y. *Tetrahedron Lett.* **1999**, 40, 9259.
- (140). Fargeas, V.; Favresse, F.; Mathieu, D.; Beaudet, I.; Chaurrué, P.; Lebre, B.; Piteau, M.; Quintard, J.-P. *Eur. J. Org. Chem.* **2003**, 1711.
- (141). Zoltewicz, J. A.; Cruskie, M. P. *J. Org. Chem.* **1995**, 60, 3487.
- (142). Zoltewicz, J. A.; Cruskie, M. P.; Dill, C. D. *J. Org. Chem.* **1995**, 60, 264.
- (143). Bennasar, M.-L.; Juan, C.; Bosch, J. *Tetrahedron Lett.* **1998**, 39, 9275.
- (144). Cho, C. S.; Motofusa, S.-i.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1995**, 60, 883.
- (145). Akiba, K.-Y.; Iseki, Y.; Wada, M. *Bull. Chem. Soc. Jpn.* **1984**, 57, 1994.
- (146). Dziedzic, M.; Malecka, M.; Furman, B. *Org. Lett.* **2005**, 7, 1725.
- (147). Meier, P.; Legraverant, S.; Muller, S.; Schaub, J. *Synthesis* **2003**, 551.
- (148). Tagawa, Y.; Yamashita, K.; Higuchi, Y.; Goto, Y. *Heterocycles* **2003**, 60, 953.
- (149). Al-Subu, M. M.; Jondi, W. J.; Dado, S. A.; Hilal, H. S. *Transition Metal Chem.* **2002**, 27, 223.
- (150). Ashimori, A.; Ono, T.; Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoyama, K. *Chem. Pharm. Bull.* **1990**, 38, 2446.
- (151). Cohen, T.; Berninger, R. W.; Woods, J. T. *J. Org. Chem.* **1978**, 43, 837.
- (152). Piazza, C.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, 41, 3263.
- (153). Numata, A.; Kondo, Y.; Sakamoto, T. *Synthesis* **1999**, 306.
- (154). Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, 124, 14844.
- (155). Brown, H. C. *J. Am. Chem. Soc.* **1960**, 681.
- (156). Miyawaki, K.; Ueno, F.; Ueda, I. *Heterocycles* **2001**, 54, 887.
- (157). Hibino, S.; Sugino, E.; Adachi, Y.; Nomi, K.; Sato, K. *Heterocycles* **1989**, 28, 275.
- (158). Frater, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, 40, 1269.
- (159). Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **1989**, 45, 479.
- (160). Oppolzer, W.; Schneider, P. *Helv. Chim. Acta.* **1986**, 69, 1817.
- (161). Oppolzer, W.; Kingma, A. J. *Helv. Chim. Acta.* **1989**, 72, 1337.
- (162). Oppolzer, W.; Dudfield, P.; Stevenson, T.; Thierry, G. *Helv. Chim. Acta.* **1985**, 68, 212.
- (163). Oppolzer, W.; Moretti, R.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, 27, 4713.

- (164). Oppolzer, W.; Moretti, R. *Tetrahedron Lett.* **1988**, 44, 5541.
- (165). Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, 25, 5885.
- (166). Takimoto, S.; Inanaga, J.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, 49, 2335.
- (167). Woodward, S. *Angew. Chem. Int. Ed.* **2005**, 44, 5560.
- (168). Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1987**, 28, 5845.
- (169). Wang, Y.; Chackalamannil, S.; Aube, J. *J. Org. Chem.* **2000**, 65, 5120.
- (170). Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, 55, 3715.
- (171). Stankovic, S.; Espenson, J. H. *J. Org. Chem.* **1998**, 63, 4129.
- (172). Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A. *PNAS* **2004**, 101, 5810.
- (173). Adam, W.; Precht, F. *Chem. Ber.* **1994**, 127, 667.
- (174). Morizawa, T.; Yasuda, A.; Uchida, K. *Tetrahedron Lett.* **1986**, 27, 1833.
- (175). Saito, H.; Hamana, M. *Heterocycles* **1979**, 12, 475.
- (176). Mallet, M.; Queguiner, G. *Tetrahedron* **1982**, 38, 3035.
- (177). Karig, G.; Thasana, N.; Gallagher, T. *Synlett* **2002**, 808.
- (178). Chandler, S. A.; Hanson, P.; Taylor, A. B.; Walton, P. H.; Timms, A. W. *J. Chem. Soc. Perkin Trans 2* **2001**, 214.
- (179). Abramovitch, R. A.; Saha, M. *Can. J. Chem.* **1966**, 44, 1765.
- (180). Stille, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923.
- (181). Sengupta, S.; Snieckus, V. *Tetrahedron Lett.* **1990**, 31, 4267.
- (182). Melnyk, P.; Gasche, J.; Thal, C. *Synth. Commun.* **1993**, 23, 2727.
- (183). Davis, F. A.; Lamendola, J.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, 102, 2000.
- (184). Taylor, E. C.; Crovetti, A. J. *J. Org. Chem.* **1954**, 19, 1633.
- (185). Green, M.; Kuc, T. A.; Taylor, S. H. *J. Chem. Soc., (A)* **1971**, 2334.
- (186). Stangler, K. J.; Tang, Y.; Anderegg, J.; Angelici, R. J. *J. Mol. Cat.* **2003**, 202, 147.
- (187). Frost, C. *Private Communication* **2004**.